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CUTANEOUS MAST-CELL TUMOURS IN THE DOG, CAT AND OX

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JUST as the appreciation of the physiological significance of the discovery of mast cells by Ehrlich in 1877 waited until 1937 for Jorpes, Holmgren and Wilander to show that these cells contained heparin and until 1952 for Riley and West to show that they contained histamine, so the first record of mast-cell tumours in dogs reported by Bashford, Murray and Cramer in 1905 lay fallow until the report of Bloom (1942) gave fresh impetus to the study of these interesting neoplasms.

This paper describes the mast-cell tumours found in the routine diagnostic material of the Royal (Dick) School of Veterinary Studies and brings up to date the series previously reported (Head, 1953). The period covered is from 1 August 1940 to 31 July 1957.

SPECIES DISTRIBUTION OF MAST-CELL TUMOURS.

The incidence of these tumours cannot be determined since there is no detailed knowledge available of the normal population from which the tumours were obtained. Some idea of the expected frequency with which such tumours may be encountered can be gained, however, from Table I. These figures are in accord with those of Nielsen (1952), Larsson (1956) and Smith and Jones (1957). It will be appreciated that mast-cell tumours are less commonly encountered in the cat than in the dog and are still less frequently seen in the ox.

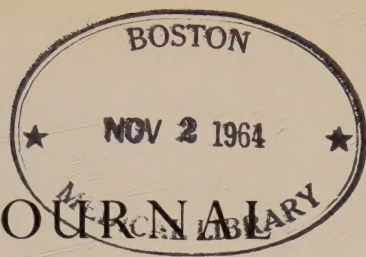


TABLE I.—*Species Distribution of Mast-Cell Tumours.*

	Dog	Cat	Ox
Total number of biopsy samples examined	5091 .	565 .	2430
Total number of autopsies performed	4412 .	1296 .	1075
Total number of mast-cell tumours diagnosed	160 .	13 .	7
Percentage of all tumour types that are mast-cell tumours	3.5 .	3.1 .	1.5
Total number of cutaneous mast-cell tumours diagnosed	152 .	9 .	5
Percentage of cutaneous and subcutaneous tumours that are mast-cell tumours	7.8 .	9.1 .	2.9

MAST-CELL TUMOUR STRUCTURAL AND BEHAVIOUR PATTERNS.

For paraffin wax sections we usually used Du Bosque fixative (picric acid-alcohol-formol) but on occasions the specimens were fixed in 10% formol saline. As well as the stains used by other workers in this field, we have used the aldehyde fuchsin method of Gomori (1950) and have found it very satisfactory. Rapid diagnosis by the imprint technique as described by Nielsen (1952) has given good results in our hands and we have also had good results from such imprints using the toluidine blue method along the lines suggested by Riley (1953) for tissue spreads, after fixation of the imprints for ten minutes in 80% alcohol.

The clinical classification, macroscopic appearance and histological findings in each of the three species are similar to those described in dog mastocytoma by Larsson (1957) and are summarized in Table II. The main difference be-

TABLE II.—*Synopsis of Tumour Patterns in the Dog.*

Character	Type of tumour					
	I (a)	I (b)	I (c)	II	III	IV
Multiplicity	Solitary or few	Solitary or few	Solitary or few	Solitary	Solitary	Very numerous
Shape	Nodular	Nodular	Nodular	Diffuse	Wound	Nodular
Size—						
Diameter	2.5 cm.	6–10 cm.	5–8 cm.	7–23 cm.	Variable	0.25–2 cm.
Thickness	1.5 cm.	5 cm.	3 cm.	3 cm.	„	0.7 cm.
Surface	Normal	Ulcerated	Ulcerated	Hairless and serum	Granulation tissue	Normal
Consistency	Firm	Soft	Firm	Soft	Firm	Firm
Encapsulation	Good	Poor	Moderate	Poor	Moderate	Good
Cut surface—						
Colour	White	White and red	White and fawn	Grey and red	Fawn and red	White
Texture	Fibrous	Cellular	Fibrous	Gelatinous	Fibrous	Fibrous
Histology—						
Mature mast cells	+++	+++	+++	++	++	+++
Immature mast cells	—	+++	+++	+++	+++	—
Collagen	+++	±	+++	+	Granulation tissue	+++
Eosinophils	—	+++	+++	+++	++	±
Oedema	—	±	—	+++	—	—
Duration in years	5	½ to 1	1 to 4	1/12 to 1	Failure of operation	2/12
Rate of growth	Slow	Fluctuating. Rapid in last 1–3 months	Steady. Rapid in last 1–3 months	Rapid in last 1–3 months	of wound to heal	Increasing in number

tween the three species is that cat tumours are smaller and ox tumours are larger than the canine mast-cell tumours.

It should be noted that the details given in this table are descriptive of the typical members of each structural pattern. As will be pointed out, there are atypical members of each group and transformation from one type to another can occur. To clarify this, each tumour type will be considered in each species. The cases are sub-divided on the basis of the tumour pattern first seen; Type III mast-cell tumours will therefore not be dealt with since they can only be encountered as a recurrence.

MAST-CELL TUMOURS IN THE DOG.

Description and Classification.

Type 1 (a) pattern.—Forty-seven dogs had tumours which macroscopically and histologically showed this pattern.

The tumours were, in the majority of cases, flattened, oval in shape and about 2.5 cm. diameter by 1 cm. thick with a range of from 0.25 cm. to 4 cm. diameter. The surface varied from normal hair coat, sparse hair coat to hairless, and in about half the cases surface ulcerations were present. The consistency was, in most cases, firm though on occasions soft. On palpation the lesions were frequently well defined. On cut surface the borders of the lesion were less clear cut than palpation had suggested but only occasionally was the edge indistinct or the cutaneous muscle involved. The cut surface was usually white but at times was yellowish-fawn and the fibrous texture of the tumour could be appreciated in the form of streaking. Histologically, the pattern observed is of aggregations of adult (heavily granulated) mast cells in thick strands of collagen fibres (Fig. 1).

Most of these tumours had been present for some considerable time (up to five years) before they were removed. In the majority of cases, some increase in size had been noted in the last six weeks before examination.

The subsequent history of twenty-three of these dogs could not be obtained.

Of those we were able to follow up, in eleven dogs no recurrences were noted, the period of observation after removal of the tumour being six months in two cases, one year in six cases and two years in three cases.

Reappearance was not noted and autopsy showed no other evidence of tumour formation in a further three dogs, two of which were destroyed eighteen months after the removal of the mast-cell tumour.

The lymph nodes draining the site of the tumour removal were involved in three dogs destroyed one month after the operation. In these instances, however, the skin wound had healed well and no recurrence at that site could be detected.

A recurrence was noted in one dog but no other lesions were found at autopsy twelve months after the removal of the Type 1 (a) tumour, the reformation being of the Type 1 (b) pattern.

Three dogs showed a reappearance of the lesion and drainage lymph-node involvement. In one dog this was seen one month after removal and the tumour changed

its pattern to Type 1 (b). In another case the tumours appeared twice at one month intervals with change of form to Type 1 (b) but no other lesions were found at autopsy. In the third case the reformed tumour was of Type 1 (c) pattern noted fifteen months after operation and on autopsy the liver, spleen and connective tissue of the pelvis of the kidney microscopically showed diffuse involvement.

Regrowth of the tumour after operation was seen in a further three dogs but no post-mortem data were available. In one of these the reappearance was at two years and one month after the operation. In another recurrences were seen at five, seven, two and five month intervals with transformation to Type 1 (b) pattern.

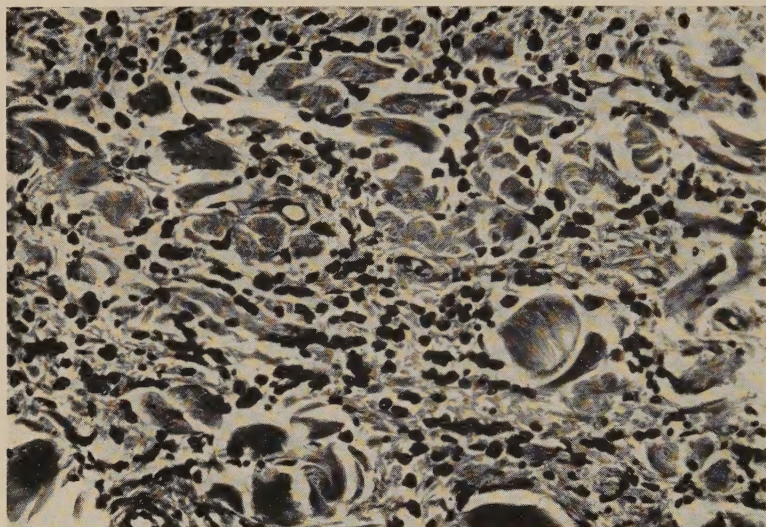


FIG. 1.—Type 1 (a) pattern tumour from the right thigh of a 12-year-old Black Labrador male dog. Note the thick collagen bundles and the darkly staining nuclei of the tumour mast cells. Paraffin section: H. & E. $\times 140$.

Type 1 (b) pattern.—Fifty-one dogs had tumours showing this pattern.

The size of these tumours was 6–10 cm. diameter and 5 cm. thick with an upper limit of 16 cm. diameter and a lower limit of 2 cm. diameter. The surface was usually sparsely hairy and in two-thirds of the cases was ulcerated. Occasionally, serum covered the free surface. A few cases appeared to have no connection with the skin, lying in the subcutaneous tissue. On cut surface the consistency was soft, often oedematous and even cystic. The tumours were white in colour with varying degrees of congestion and haemorrhage. Little or no structural pattern could be appreciated on cut surface and examination confirmed the evidence derived from palpation that the degree of encapsulation was poor, penetration to the underlying muscle being common. On histological examination, there were numerous mast cells with varying degrees of granulation and many eosinophils supported by delicate reticulin network (Fig. 2).

These tumours were usually presented with the history that they had been

noticed for six months to a year and then had rapidly increased in size in the last one to three months. Some tumours had a history of fluctuation in size before the final rapid increase in dimensions.

No subsequent history could be obtained in seventeen cases.

Recurrence was not seen in nine cases—for five years in one dog, three years in one dog, one year in four dogs and six months in the remaining three dogs.

One dog showed no reformation at the first site of removal ten months after this removal but developed seven new Type 1 (a) tumours at different sites. This dog, however, was not available for further examination.

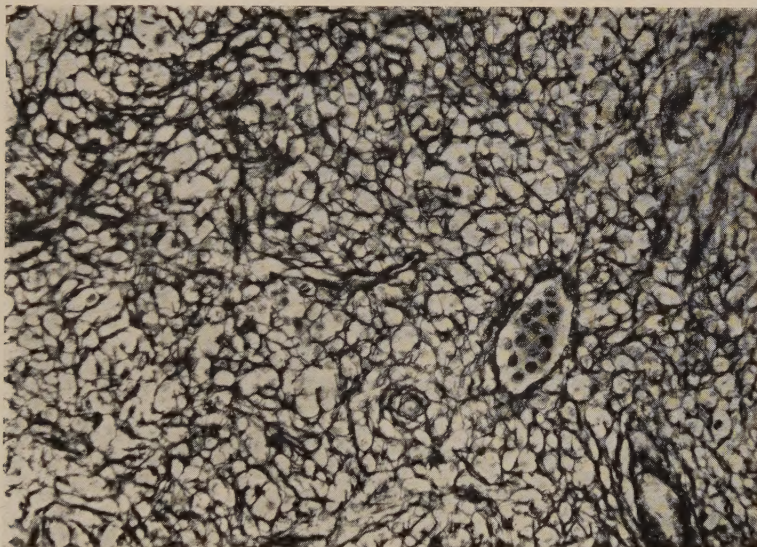


FIG. 2.—Type 1 (b) pattern tumour from the perineal region of a 7-year-old Terrier male dog. Note the well developed reticulin network surrounding the tumour cells and the small amount of collagen present. Paraffin section: Gordon and Sweet's method. $\times 140$.

Post-mortem examination failed to reveal any other lesion in three dogs which showed no recurrence over a period of five months.

Involvement of the lymph node draining the site of removal, despite the absence of regrowth of the tumour five months or more after the operation, was seen in six dogs and in two of these cases the spleen and in one also the liver showed involvement in the disease process.

Recurrences at intervals of from six to fourteen months were seen in five dogs, all these being of Type 1 (b) pattern but no post-mortem examination was permitted.

Two dogs showed reappearance of the tumour and tumour cells in the drainage lymph node. In one case, six weeks after the first removal, the recurrence was of Type 1 (b) structure. In the second case the tumour grew again one month after the first removal and was of the original type, by which time another tumour of Type 1 (b) had formed. This was also removed but returned in the Type 1 (b) pattern six weeks after its removal.

Eight further dogs showed a reappearance of the tumour and at autopsy other

organs were found to be involved. In three of these cases which showed the Type 1 (b) structure one month after the first removal, the drainage lymph node, liver and spleen were included in the disease process. In one dog the operation wound failed to heal (that is, a change of tumour pattern to Type III) and at autopsy one month later the drainage lymph node and spleen were seen to be affected. In two dogs where the reformed tumour was noted two months after operation, the drainage lymph node, liver and spleen were involved and solitary metastases were noted in the lung (2 cm. and 0.25 cm.). In one case the recurrence was of Type 1 (b), in the other of the Type 1 (c) and a new tumour of Type II had also developed. In one dog the tumour showed a reappearance at six weeks and again at eight weeks after the second removal (both recurrences being of Type 1 (b)) and at autopsy the drainage lymph node, liver and spleen were involved. The last dog in this series, when destroyed because of a Type 1 (b) recurrence, showed tumour cells in the liver, spleen and the connective tissue of the pelvis of the kidney but not in the drainage lymph node.

Type 1(c) pattern.—Fifty dogs had tumours showing this pattern when first examined.

These tumours were usually 5 to 8 cm. diameter and 3 cm. thick but sometimes were 3 cm. diameter and very rarely larger than 8 cm. diameter. The surface was as recorded in Type 1 (a) tumours but more than two-thirds of the cases showed extensive ulceration with serous exudate in some instances. A few were subcutaneous with apparently no connection to the overlying skin. Their consistency was firm and on cut surface they were white or fawn in colour, rarely haemorrhagic or yellow. Usually there was a moderately distinct capsule on the deep surface which was often slightly oedematous but occasionally penetration to the muscle was seen. Histologically, the pattern was as in the Type 1 (a) tumours but with more poorly granulated immature mast cells and a larger number of eosinophils.

The duration of the tumours was of the order of one to four years with recent rapid growth over the last one to three months.

In thirty-three dogs no follow-up history could be obtained.

No recurrence was seen in four dogs over periods of from six months to two years after operation. Originally these dogs had solitary tumours in two cases, two tumours of Type 1 (c) in one case, while one dog had a tumour of three years' duration and another a tumour of two months' duration—both of Type 1 (c) pattern.

Two dogs showed a reappearance of Type 1 (c) structure two months after operation but no post-mortem examination was allowed.

One dog showed a return of the tumour similar in character within a month of the first operation and a new tumour of the Type 1 (a) configuration developed during the same period; one month after the operation a Type II tumour appeared at the original site but no further follow-up history was available.

Three dogs showed recurrence and tumour mast cells in the drainage lymph node within two months of the first removal but no autopsy was permitted: in two of these cases, the reformed tumour was of Type 1 (c), whereas in the other, it was of Type 1 (b) in character.

In one dog the wound failed to heal (transformation to Type III pattern) and a new tumour of Type 1 (a) developed as well as lymph-node involvement.

One dog showed re-appearance of a Type 1 (b) pattern three months after removal of the Type 1 (c) tumour and the drainage lymph node became diseased.

In two dogs tumours were found again at two months after operation and a second tumour growth developed at two and five months respectively, all tumours being of the Type 1 (c) pattern and on autopsy both showed inclusion of drainage lymph node, liver and spleen in the disease process.

In one dog, similar disease lesions were found in the drainage lymph node, spleen and liver at autopsy when a reformation of Type 1 (c) structure was noted three months after the first operation.

Drainage lymph node, liver and spleen involvement was found in one dog which showed a recurrence after seven months, this being of Type 1 (c) pattern and simultaneously three new Type 1 (a) tumours had developed.

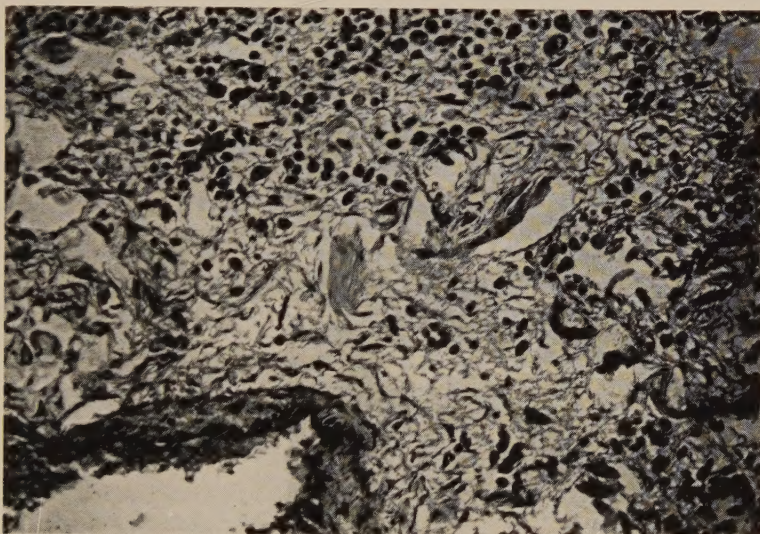


FIG. 3.—Type II tumour from the prepuce and thigh region of a 6-year-old Golden Cocker Spaniel illustrating the oedematous nature of the stroma. Paraffin section: H. & E. $\times 140$.

The last dog in this series showed a minute re-appearance of Type 1 (c) pattern fifteen months after the first operation and on autopsy the spleen was the only other organ to be involved.

Type II pattern.—Only four dogs showed this pattern from the inception of the disease. In two cases the lesions measured $7 \times 5 \times 2.5$ cm. and in the other two cases, they measured $23 \times 20 \times 3$ cm. The skin overlying the tumours was at first normal, then became hairless and moist. The cut surface showed oedema with no clear cut borders in the subcutaneous connective tissue but the tumour did not invade the muscle. On histological examination, the structure resembled that seen in Type 1 (b) tumours but with more oedema (Fig. 3). In two cases the duration of the lesion was one month of rapid growth. In the third case it was over six months, having rapidly grown from two small ulcerated

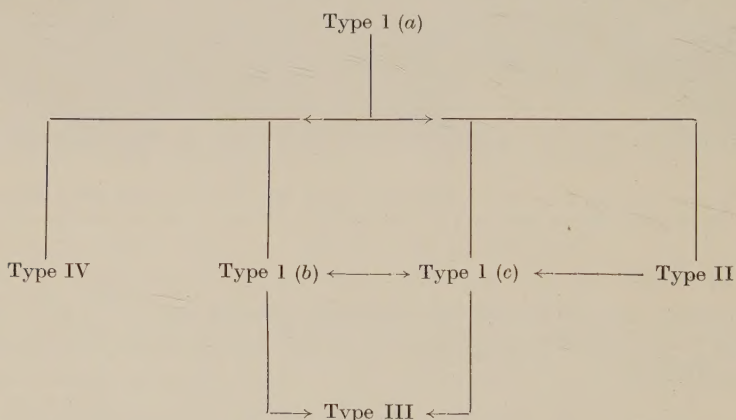
lesions, and in the fourth case had been present for one year with terminal rapid growth.

In none of these dogs was surgical intervention considered feasible and all were autopsied. The drainage lymph nodes and spleen were involved in all instances, the liver in two cases (one of which showed foci up to 0.5 cm. diameter and the other was seen to be involved histologically). One dog showed a 0.25 cm. nodule in the heart muscle and another exhibited multiple 0.2 cm. nodules throughout the lungs. The tumours were solitary in two cases and in the other two cases multiple nodules of other types developed after the Type II lesions had been noted. One dog showed three Type I (c) tumours of one month's duration. The other showed four Type I (a) lesions of one month's duration.

Type IV pattern.—One dog showed multiple plaque-like formations all over the body (more than a hundred in number), these lesions having developed two months after the removal of a solitary Type I (a) tumour in a manner similar to that described in Bloom's case No. 4 (1942). The plaques, which ranged from 0.25 cm. diameter to 2 cm. diameter by 0.7 cm. thick, were of the Type I (a) pattern. The dog was not available for post-mortem.

INTER-RELATIONSHIP OF THE VARIOUS TYPES.

The above types are structural and behaviour patterns of one tumour—not water-tight, separate classes of tumour. Thus, as pointed out by Larsson (1957) they can change into one another as shown below :—



This change in type has been demonstrated by an alteration in character of the recurrence as well as by clinical history in all cases except the transformation of the Type I (a) to Type II which rests on history alone. Larsson also mentions change from Type II to Type III—an observation we have not yet been able to support.

In addition to suggesting that Type IV should be considered as a separate pattern, we have noted the development of multiple tumours after one or more tumours were first noted (Table III).

TABLE III.—*Development of Multiple Mast-Cell Tumours.*

Primary tumour.	Tumour subsequently formed.			
	1 (a).	1 (b).	1 (c).	II.
Type 1 (a) . .	+	..	..	..
Type 1 (b) . .	+	+	..	+
Type 1 (c) . .	+	..	+	..
Type II . .	+	..	+	..

MULTIPLICITY.

Our figures for the percentage of tumours which are multiple are lower than that given by Nielsen (1952) of 26% and by Larsson (1957) of 48.3%, but are higher than Mulligan's (1949) figure of 6%. It seems from Table IV to be a trend that more malignant tumours, i.e. Types 1 (b), 1 (c) and II tend to become multiple.

TABLE IV.—*Multiplicity of Mast-Cell Tumours.*

Type	1 (a)	1 (b)	1 (c)	II	Total
Solitary	45	44	44	2	135 (89%)
Multiple	2	7	6	2	17 (11%)
Total number of dogs .	47	51	50	4	152

Like Larsson (1957), however, we cannot agree with the statement of Oliver *et al.* (1947) that multiple mastocytomata are malignant in contrast to solitary ones (Tables V, VI and VII).

RECURRENCE AFTER SURGICAL REMOVAL.

All patterns of mast-cell tumours on histological examination have indistinct borders, strands of tumour cells penetrating the surrounding connective tissue for some distance from the main mass (Fig. 4).

Recurrence at the site of operation occurred in nearly half the cases we were able to follow up (Table V). This is far higher than the figures given by Nielsen

TABLE V.—*Recurrence after Surgical Removal.*

Pattern of tumour originally removed.	Time after operation.				Total number of dogs.
	0-3 months.	4-9 months.	10-12 months.	Over 12 months.	
<i>Type 1 (a)—</i>					
No recurrence .	4	2	6	4	16
1st "	2	1	1	2	6
2nd "	2	1	..	..	..
3rd "	1	..	..	..	..
4th "	..	1	..	..	..
<i>Type 1 (b)—</i>					
No recurrence .	..	12	..	7	19
1st "	10	3	..	2	15
2nd "	2	..	..	..	..
<i>Type 1 (c)—</i>					
No recurrence .	..	1	..	3	4
1st "	9	3	..	1	13
2nd "	1	1	..	..	..

(1952) of one-third or by Larsson (1957) of 10% of operated cases. This may be due to our inability to trace the history in successfully operated cases or may in some measure be due to the fact that ample excision of apparently healthy surrounding tissue was not, in some of our cases, made (a point stressed by Larsson). It should be noted, however, that we encountered proportionately more of the Type 1 (b) and Type 1 (c) cases than Larsson and these are the types of tumour which tend to recur. The recurrences are most often seen within the first three months after operation but may be encountered even after twelve months of apparent success.

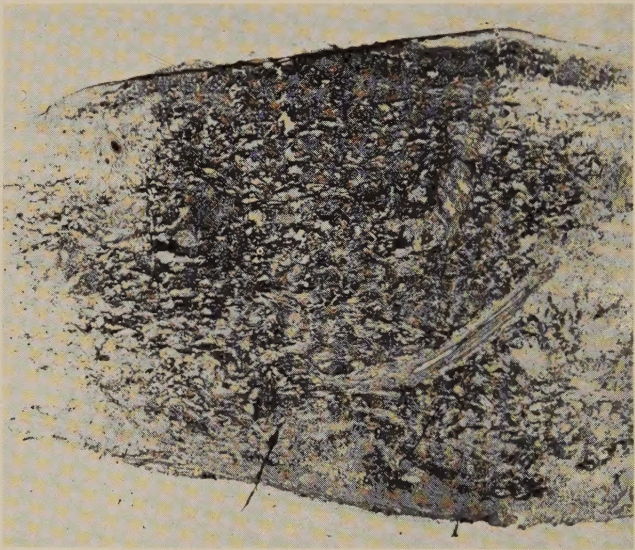


FIG. 4.—Type 1 (c) pattern tumour from the scrotal region of an aged Bull Mastiff male dog. Note the poorly defined border of the tumour, strands of tumour cells running for some distance into the surrounding connective tissue. Paraffin section : H. & E. $\times 11$.

INVOLVEMENT OF DRAINAGE LYMPH NODES.

Of the dogs examined at post-mortem, 75% showed involvement of the drainage lymph nodes (Table VII).

TABLE VI.—*Involvement of the Drainage Lymph Node in Various Types of Mast-Cell Tumours.*

	Types of tumour.				Total
	1 (a).	1 (b).	1 (c).	II.	
No L.N. involvement	4	4	1	0	9
L.N. sinuses involved	3	9	2	2	16
L.N. metastases	3	6	8	2	19
Total	10	19	11	4	44

In the cases in which this examination could be made from either biopsy or autopsy specimens, we found 80% of the dogs showed lymph-node involvement (Table VI). The first lymph node to be affected is that draining the tumour. Subsequently, further lymph nodes in the lymphatic chain are involved in two-thirds of the cases. This usually implies spread from the superficial inguinal lymph node to the iliac lymph node but sometimes from the axillary lymph node to the prescapular, as reported by Chambers (1931) and Nielsen (1952). The lymph node is first involved by infiltration of the sinuses (as reported by Mulligan, 1949), then the lymphoid tissue atrophies (as reported by Hangartner, 1949) and finally there is replacement of the normal architecture by true metastases. This phenomenon of lymph-node involvement is of interest when correlated with the findings of Arvy (1956) that in rats treated with the histamine-liberator compound 48/80, the mast cells leave the connective tissue and drain to the lymph node where they undergo lysis, suggesting to her that the lymph node is the normal centre of lysis of mast cells at the end of their life cycle.

INVOLVEMENT OF OTHER TISSUES.

Of the dogs examined at post-mortem, 55.5% showed splenic involvement (Table VII)—a phenomenon noted previously by Bloom (1942), Mulligan (1949) and Nielsen (1952). Our findings agree with Bloom in that the mast cells were found in both focal and diffuse patterns and support Mulligan's description that the mast cells frequently lie in the sinuses round the white pulp. This involvement is seldom appreciated on macroscopic examination although the spleen may be visibly enlarged.

TABLE VII.—*Involvement at Autopsy of other Tissues in Cutaneous Mast-Cell Tumours of Dogs.*

Site involved.						Type of tumour.				Total.
						I (a).	I (b).	I (c).	II.	
No lesions	.	.	.	.	.	4	3	..	..	7
L.N.	..	..	..	..	..	1	4	4	..	9
L.N.	Spleen	..	..	..	..	..	2	1	1	4
L.N.	Spleen	Liver	..	..	..	..	5	3	1	9
L.N.	Spleen	Liver	Kidney	..	..	1	..	..	..	1
			Pelvis							
L.N.	Spleen	Liver	..	Lung	..	..	2	..	..	2
L.N.	Spleen	Liver	..	..	Heart	..	..	..	1	1
L.N.	Spleen	..	..	Lung	..	..	..	..	1	1
..	Spleen	..	..	..	..	..	..	1	..	1
..	Spleen	Liver	Kidney	..	..	..	1	..	..	1
			Pelvis							

Similarly, we have found, as did the above mentioned authors, involvement of the liver in 38.9% of autopsy cases. In the majority of cases, this consisted of periportal aggregations of mast cells as described by Bloom, but in one case 1 cm. diameter focal lesions were found, as reported by Mulligan.

Involvement of the lung has been previously observed by Bloom and Nielsen and was present in 8.3% of our post-mortem cases. These lesions were solitary in two cases (2 cm. and 0.25 cm. diameter) and multiple in one case (0.2 cm. diameter).

Larsson (1957) referred to one case of infiltration of heart muscle by mast cells and we encountered one case with a solitary 0.25 cm. diameter lesion (2.8% of autopsy cases).

The connective tissue of the pelvis of the kidney was, on histological examination, found to be infiltrated by mast cells in two dogs (5.5% of autopsy cases).

AGE, BREED AND SEX DISTRIBUTION.

In order to assess the breed, sex and age distribution of canine mast-cell tumours, some attempt has to be made to relate the observed tumour cases to the general population. Since in the United Kingdom owners are licensed to keep dogs rather than dogs being licensed to be kept, there is no simple method of accurately enumerating the general population. In the subsequent analyses, some estimate of the general population was made by using the figures for all dogs examined during 1957 at the School's clinic, whatever the reason for examination ($n = 5,678$). To these totals were added the figures for all dogs autopsied or from which biopsies were examined during the period 1 August 1941 to 31 July 1953 ($n = 4,327$). It was thought advisable to use the sum of both these groups to compensate for changes over the years in dog owners' preferences for certain breeds or sexes. In point of fact, the sex and age distribution of these two groups remained constant, only the breed distribution altering with fashion. This estimate of the general population is called the "Sample Normal Population" in the following analyses.

TABLE VIII.—*Age Distribution of Dogs with Mast-Cell Tumours.*

Age. (Years.)	Type 1 (a). $n = 39$.	Type 1 (b). $n = 46$.	Type 1 (c). $n = 46$.	All types (including Types II and IV). $n = 137$.
1	3	0	0	3
2	0	0	0	0
3	2	1	1	4
4	2	1	0	3
5	5	6	6	18
6	2	8	3	15
7	9	6	5	20
8	3	4	3	10
9	4	9	3	16
10	6	3	11	21
11	0	2	5	7
12	3	2	7	14
13	0	2	1	3
14	0	2	1	3

$\bar{x} \pm e$ 7.00 $\pm$ 1.49 8.04 $\pm$ 1.25 8.98 $\pm$ 1.24 8.08 $\pm$ 0.77

The mean age of the sample normal population was 4.91 ± 0.04 years.

Age distribution.—The age distribution of dogs with mast-cell tumours is summarized in Table VIII. The term “age” here is used to refer to the age of the dog at the time of histological diagnosis of the tumour, that is at first surgical removal or, in cases where no operation was attempted, at post-mortem. The high mean age of the dogs with mast-cell tumours when compared with the mean age of the sample normal population is statistically significant and is comparable with the figures given by Larsson (1957). No statistical difference could be detected between the mean age of dogs with tumours of Type 1 (a) pattern compared with the dogs having tumours of Type 1 (b) pattern, or Type 1 (a) compared with Type 1 (c) when subjected to the t-test. Since the figures in Table VIII appear to show a bias towards the younger age groups in Type 1 (a) cases and towards the older age groups in Type 1 (c) cases, it was decided to use the chi-square analysis as a more sensitive method of testing this hypothesis. Table IX shows the results of this analysis.

Once again, although the hypothesis is strengthened by a trend in the chi-square values, none of the individual values are statistically significant (d.f. = 8), though the value of the sum of the chi-squares (d.f. = 1) is statistically significant showing that the samples were taken from a heterogeneous population. The failure to demonstrate this correlation between age and type may be due to there being too few cases in certain cells in the table, for example 10-year-old dogs with Type (b) tumours in Table IX.

TABLE IX.—*Age Distribution of Dogs with Mast-cell Tumours correlated with Tumour Type.*

Age (years).	Dogs with Type 1 (a) tumour.			Dogs with Type 1 (b) tumour.			Dogs with Type 1 (c) tumour.			Total all types.
	Number	Number	χ^2 -value.	Number	Number	χ^2 -value.	Number	Number	χ^2 -value.	
	Ob- served.	Ex- pected.		Ob- served.	Ex- pected.		Ob- served.	Ex- pected.		
0-5	12	8.04	1.95	8	9.48	0.23	7	9.48	0.65	27
6 and 7	11	9.82	0.14	14	11.58	0.50	8	11.58	1.11	33
8 and 9	7	7.74	0.07	13	9.13	1.64	6	9.13	1.07	26
10	6	5.95	0.00	3	7.02	2.30	11	7.02	2.26	20
11-14	3	7.45	2.66	8	8.79	0.07	14	8.79	3.09	25
Total	39	39.00	4.82	46	46.00	4.74	46	46.00	8.18	131
Total χ^2 -value										17.74

Breed distribution.—The breed distribution figures are summarized in Table X where it will be seen that the Bull Terrier and Boxer are highly over-represented, the Scottie is over-represented and the Alsatian is under-represented. The predisposition of the Boxer to mast cell tumours has already been demonstrated by Larsson (1957) who has pointed out that such predispositions should be correlated with the mean age of the breeds in the general population. Unfortunately we were not able to apply such a correction to our figures.

TABLE X.—*Breed Distribution of Dogs with Mast-Cell Tumours.*

Breed (pedigree and related crosses).	Number of dogs in sample normal population. $n = 10,005$.	Number of dogs with mast cell tumours.		χ^2 - value (d.f. ¹ = 1).
		Observed. $n = 148$.	Expected.	
Bull Terrier and Staffordshire Bull Terrier	150	17	2.22	91.85*** ²
Boxer	239	14	3.53	28.16*** ²
Scottish Terrier	392	13	5.80	7.74*** ²
Retriever and Labrador	857	20	12.68	4.20*
Yorkshire Terrier	85	3	1.26	1.22 ²
Spaniel	1,219	21	18.03	0.50
Kerry Blue Terrier	20	2	0.30	0.48 ²
Fox Terrier	352	7	5.21	0.32 ²
Irish Setter	56	1	0.83	0.13 ²
Bull Mastiff	27	1	0.40	0.00 ²
Great Dane	33	1	0.49	0.00 ²
Irish Terrier	27	1	0.40	0.00 ²
Bulldog	68	1	1.01	2.57 ²
Terrier	1,760	25	26.03	0.04
Airedale Terrier	99	1	1.46	0.63 ²
Dachshund	139	1	2.06	1.18 ²
Poodle	256	2	3.79	1.38 ²
West Highland White Terrier	205	1	3.03	2.11 ²
Cairn Terrier	447	3	6.61	2.55
Collie	1,363	12	20.16	3.33
Alsatian	786	1	11.63	9.72 ²
Other breeds	1,425	0	21.08	—

¹ d.f. = degrees of freedom.² This value is a corrected χ^2 - value (Yates's correction).

* = probably significant.

** = statistically significant.

*** = highly statistically significant.

Sex distribution.—The sex distribution of dogs with mast-cell tumours is shown in Table XI. The absence of a sex predisposition agrees with the results of Larsson (1957) but is contrary to those of Nielsen (1952) who found a predisposition to males and Mulligan (1949) who found a predisposition to females.

TABLE XI.—*Sex Distribution of Dogs with Mast-Cell Tumours.*

Sex.	Number of dogs in sample normal population.	Number of dogs with mast-cell tumours		χ^2 - value (d.f. = 1).
		Observed.	Expected.	
Male	5653	83	86.2	0.12
Female	3854	62	58.7	0.18
Total	9507	145	144.9	

Site distribution. There is some evidence to suggest that cutaneous mast-cell tumours occur most commonly on the hindquarters of dogs (Mulligan, 1949; Nielsen, 1952; Larsson, 1957) and are rare on the extremities (Oliver *et al.*, 1947). Our findings support these observations on trends of localisation as is shown by the following figures for all types of tumours except Type IV. The

sites of primary tumours and tumours developing after the primary at new sites are recorded but recurrences of primary tumours are not included :

23 cases in head and neck (12·9%)	7 face, 4 earflap, 5 lip, 7 neck.
31 cases in forelimb (17·4%)	5 brisket, 9 shoulder, 9 elbow to carpus, 5 carpus to foot, 2 foot, 1 unknown site.
32 cases in the dorsolateral trunk (18%)	15 chest, 10 flank, 7 back.
68 cases in hindlimb (38·2%)	1 tail, 8 peri-anal region, 1 vulva, 17 rump, 35 stifle to tarsus, 1 tarsus to foot, 2 foot, 3 unknown site.
24 cases in ventral abdomen (13·4%)	16 mammary region, 8 prepuce and scrotum.

This distribution is of interest when viewed in the light of the distribution of normal mast cells in the dog. Arvy and Quivy (1955) have shown that the lip and earflap in the newborn puppy are rich in mast cells while, in the adult canine, the connective tissue of the mammary glands (especially in old bitches) and the prepuce contain many of these cells. Obviously, more work is needed to correlate the changes in the normal mast-cell population at different sites of the skin with the age of the dog.

RELATED LESIONS IN SITES OTHER THAN THE SKIN.

Mulligan (1949) has mentioned that the mesenteric and mediastinal connective tissue may show mast-cell tumour formation. We have found eight cases in which only tissues other than the skin were affected. These cases have not been included in the above analysis :—

- (i) Mesenteric lymph node in a 2-y.o. Staffordshire Bull Terrier dog and a 7-y.o. Collie dog.
- (ii) Mesenteric lymph node and spleen in a 3-y.o. Springer Spaniel dog.
- (iii) Mesenteric lymph node, spleen and liver in a 7-y.o. Alsatian dog and a 7-y.o. Terrier dog.
- (iv) Mesenteric lymph node, lymph nodes of the chest and foci in the kidney of a 7-y.o. Retriever dog.
- (v) Periosteum and synovial membranes of the femoro-tibial joint of an 8-y.o. Spaniel dog.
- (vi) Tongue of a 7-y.o. Shetland Collie bitch.

We also encountered a case showing multiple tumours in the skin and subcutis in which similar foci were present in the sternal lymph node, mesenteric lymph node, bronchial lymph node, pancreas, testis, omentum, heart, pleura, diaphragm and bone marrow. Many of the cells in this tumour were lobulated and showed fine granules with Leishman stain, ranging from neutrophilic to basophilic in their reaction. This we tentatively classified as myeloid leukaemia rather than mast-cell sarcoma although the absence of involvement of liver and spleen is peculiar (Meier, 1957a).

MAST-CELL TUMOURS IN THE CAT.

Type 1 (a) pattern.—Three cases of this pattern were seen. A 2-y.o. castrated male cat showed a 2 cm. diameter $\times$ 0·25 cm. thick ulcerated tumour on the

undersurface of the third digit of the foreleg. Three 1 cm. diameter $\times$ 0.25 cm. thick ulcerated tumours were found in the inguinal region of a castrated male cat. Similar ulcerated lesions were found in the skin of the hind leg of a 5-y.o. Tabby male cat, the exact number not being stated. Neither duration times nor follow-up histories were available in these cases.

Type 1 (b) pattern.—The only difference between these tumours in the cat and those in the dog was that in the cat they were smaller (from 2 to 4 cm. diameter and from 1 to 2 cm. thick) and on cut surface they appeared grey rather than white. Of the other three cases of this type one was removed from just above the right eye of a 3-y.o. black Persian male cat and had a history of fluctuation in size. The second case showed two lesions but no further details were available. The third case in a 9-y.o. female cat was located below the conjunctiva of the left lower eyelid and was of two months' duration. In this third case a recurrence was noted of the Type 1 (b) pattern within a week of operation and at autopsy (the only case of this pattern with a follow-up history) the sub-maxillary and retropharyngeal lymph nodes showed sinus involvement, the liver showed periportal mast-cell infiltration and the red pulp of the spleen was rich in mast cells.

Type 1 (c) pattern.—This pattern was seen in two ulcerated tumours, 3 cm. diameter $\times$ 0.5 cm. thick, located on the inner aspect of the elbow of an 8-y.o. black male cat. The lesion had been present for one month and at post-mortem examination the axillary lymph node (sinuses only), portal tracts of the liver, and red pulp of the spleen showed involvement in the disease process.

Type IV pattern.—Two cases were seen in which numerous 1.5 cm. diameter $\times$ 0.5 cm. thick ulcerated lesions were found all over the body except on the muzzle, pads of the feet and ear flaps. The lesions were most numerous over the head, neck and shoulder and least noticeable on the ventral abdominal skin. Their duration was given as six weeks. On autopsy the first, a 5-y.o. black and white female cat (2 weeks pregnant), also showed involvement of the sinuses of the superficial lymph nodes with atrophy of the lymphoid tissue, periportal infiltration of the liver and numerous mast cells in the red pulp of the spleen. The autopsy of the second, a 3-y.o. black castrated male cat showed a similar involvement of other tissues, and small groups of mast cells were found round the bronchi on histological examination.

DISTRIBUTION

The number of cases encountered was too few to attempt an analysis of breed, sex and age distribution. Our cases appear to confirm the suggestion made by Meier (1957b) that feline mast-cell tumours have a different site distribution from that seen in the dog—that is, they tend to occur on the head and neck rather than on the hindquarters.

BEHAVIOUR.

Feline cutaneous mast-cell tumours appear to be multiple more often than their canine counterparts and on the basis of this small series it seems that involvement of the internal organs is common.

RELATED LESIONS IN SITES OTHER THAN THE SKIN.

Meier and Gourley (1957) in a report of basophilic (myelocyte) or mast-cell leukaemia in the cat summarized the few reports of this type of lesion which are present in the literature. Stünzi (1956) also reported an instance of mast-cell leukaemia in a cat. We have encountered four cases of this type all in castrated male cats, three of them being 9-y.o. and the fourth being 11-y.o. In two of these animals only the spleen and liver were sent for examination, while the other two examples were found at post-mortem. In all four cats the red pulp of the spleen and the periportal regions of the liver were heavily infiltrated by mononuclear cells with numerous large basophilic granules. In the cases found at autopsy, the portal and mesenteric lymph nodes also showed numerous mast cells in the sinuses. Unfortunately, peripheral blood examination was not performed.

One 12-y.o. black castrated male cat showed a somewhat similar picture in the liver, spleen, sternal and renal lymph nodes with focal lesions in the pericardial sac, heart and kidney. Romanowsky stained sections of these tissues, however, did not reveal clear cut basophilic granulation as in the preceding cases but showed the granules to be predominantly neutrophilic; we therefore classified this case as one of myelogenous leukaemia. There are many similarities between this case and the one reported by Meier and Patterson (1956) although unfortunately no examination of the peripheral blood was made in our case.

MAST-CELL TUMOURS IN THE OX.

Type 1 (a) pattern.—In one case multiple 3 cm. diameter $\times$ 1 cm. thick ulcerated lesions (the exact number not stated) were present on the head, thorax and abdomen of a Friesian calf. No duration or follow-up history was available. The second case was found on post-mortem of an adult Ayrshire cow which showed two subcutaneous lesions 2 cm. diameter on the flank, one on the skin of the right hind quarter of the udder, and a 6 cm. diameter nodule over the chest. The udder showed numerous 0.25 to 5 cm. diameter nodules scattered throughout and four slightly larger nodules were present in the wall of the uterus. There were two 2 cm. diameter $\times$ 1 cm. thick plaque-like lesions under the peritoneum of the left flank. The prescapular, iliac and supramammary lymph node sinuses were considerably distended by mast cells. This case resembles that demonstrated by Greig (1950).

Type 1 (b) pattern.—A 5-y.o. cow exhibited a 12 cm. diameter subcutaneous

nodule of six weeks' duration at the root of the tail. No follow-up history was obtained.

Type 1 (c) pattern.—An adult Shorthorn cow showed a recurrence of this type three months after the first removal from the axilla and two months later numerous 1.5 cm. diameter $\times$ 0.5 cm. thick nodules appeared in the axilla, thighs, udder and anal region. On post-mortem examination, numerous 1 cm. diameter nodules were present in the spleen, omentum and mesentery and a 0.5 cm. diameter nodule was found in the cortex of the kidney.

Type IV pattern.—A Shorthorn calf, when six months old, developed numerous nodules all over the skin. These plaques, which were often ulcerated, ranged from 0.5 cm. to 1 cm. in thickness and were from 0.5 to 7 cm. diameter. The lesions remained visible over the following five years, during which time the cow has had two calves and has kept in good health.

DISTRIBUTION AND BEHAVIOUR.

From this small series, three facts emerge. First, that these tumours are often subcutaneous; second, that they are often multiple; and third, that internal involvement is common.

RELATED LESIONS IN SITES OTHER THAN THE SKIN.

Monlux *et al.* (1956) mentioned two tumours (in the spleen, and skeletal muscle) composed of cells having similar morphology to mast cells and stated "Whether these two tumours are true mast-cell sarcomas or myeloid tumours is debatable." Smith and Jones (1957) noted the presence of mast-cell tumours in the omentum of the bovine. We have seen two cases of mast-cell tumours not involving the skin. One of these occurred in the chest cavity of an 18-m.o. Ayrshire heifer. The other was found in the lung, uterus, the peritoneum of the flank, cranial cavity, the supramammary, renal, mesenteric and mediastinal lymph nodes of a 2-y.o. Ayrshire heifer.

Three cases of myeloid leukaemia arising from the vertebrae were encountered—one case in a heifer and two cases in 2-y.o. bullocks. A similar pattern was observed in a tumour from the pelvis of a 2-y.o. Hereford heifer.

NOMENCLATURE.

The nomenclature of these mast-cell lesions needs some clarification. Hantgartner (1949) believed that these lesions did not represent true neoplasms but were a type of infectious granuloma. The reticular hyperplasia and plasma-cell infiltration in the lymph nodes, spleen and liver and the granuloma-like proliferation in the kidney with multinuclear giant cells were not seen in our cases and I consider that the lesions should be regarded as neoplasms.

Köhler (1954) also discussed this point and reached the conclusion that there

may be besides the true mastocytoma, a chronic inflammatory process rich in mast cells, this inflammatory reaction being of unknown aetiology. Bloom (1942), Nielsen (1952), Stünzi (1955) and Larsson (1957) referred to these tumours as "mastocytoma", whereas Mulligan (1949) used the term "mast-cell sarcoma". Undoubtedly, in cases which do not recur and do not involve the drainage lymph nodes or other tissues, "mastocytoma" seems to be the correct term. Bloom (1942) considered that the lymph-node lesions in his series might have been metastatic but that involvement of tissues with a normal mast-cell population represented multifocal origin. I agree with this concept. Where there is a recurrence and lymph-node metastases and even involvement of internal organs, the term "mast-cell sarcoma" is preferable to "mastocytoma".

Based on the evidence presented above it appears that this group of neoplasms can be sub-divided into :—

- (A) Those occurring in the skin and subcutis ;
- (B) those occurring in other organs.

Furthermore, each of these sub-divisions can be separated into :—

- (i) A benign form—the mastocytoma ;
- (ii) a malignant form—the mast-cell sarcoma showing invasive growth, metastases and systemic involvement (usually of the liver and spleen).

Certainly, in the canine tumours, cutaneous mast-cell neoplasms are not terminal metastases from an internal disease spreading to involve the skin, since cutaneous mastocytoma are more common than the internal group of mast-cell neoplasms. Our series of feline and bovine mast-cell tumours fall into line with this nomenclature : but the problem of the relationship between mast-cell sarcoma involving organs other than the skin and basophil cell leukaemia is accentuated in the cat and ox because of the large number of cases in this second group. Cutaneous mast-cell sarcoma can be easily separated from basophil cell leukaemia on the basis of the absence of bone-marrow and peripheral blood involvement in the former cases. Whether internal mast-cell sarcoma and basophil leukaemia are one and the same disease is bound up with the question of the relationship between the blood basophil and the tissue mast cell. Too few cases have been seen to enable us to decide whether basophil cell leukaemia forms a distinct group based on behaviour pattern or merely are a tinctorial class within the myeloid leukaemias.

SUMMARY.

A description is given of the cutaneous mast-cell tumours encountered in 152 dogs, 9 cats and 5 oxen.

A minority of mast-cell tumours involve only internal organs. This was seen in 8 dogs, 4 cats and 2 heifers.

Based on the above investigations, the following classification and nomenclature for mast-cell tumours is suggested :

(A) Tumours involving the skin and subcutis in which six structural patterns are shown—Types 1 (a), 1 (b), 1 (c), II and III, after Larsson (1957) and a further variety, Type IV.

(i) Cutaneous mastocytoma ;

(ii) cutaneous mast-cell sarcoma, with or without systemic involvement.

(B) Tumours involving internal organs only.

(i) Internal mastocytoma ;

(ii) internal mast-cell sarcoma.

This classification is tentative since considerably more work is needed on the blood and bone-marrow changes, especially in cases of mast-cell tumours involving internal organs only.

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PHARMACOLOGY OF THE TISSUE MAST CELL

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ALTHOUGH mast cells have been the subject of numerous publications since they were first clearly described by Ehrlich 80 years ago, it is only recently that they have come to interest the pharmacologist. Ehrlich (1877) gave a description of their morphology, staining properties and distribution and then left it to others to elucidate the chemical nature of the granules these cells contain. Some 60 years after Ehrlich's time, Jorpes and his colleagues (1937) in Stockholm found that heparin, a powerful anticoagulant material isolated from dog liver, stained metachromatically with toluidine blue, and they searched the tissue for metachromatism as a possible clue to the site of formation of heparin. Thus it was that Jorpes was able to show that there is a good correlation between the mast-cell count of a particular tissue and the amount of heparin that can be extracted from it. It was thought that mast cells are perivascular in location so that they can produce heparin and pour it into the blood stream. But a later study of the movement of the perivascular mast cells reveals that they migrate *away* from the blood vessels and hence they probably produce their secretion for both blood and tissues. Their function may be less concerned with blood clotting than with the maintenance and repair of the connective tissue.

The discovery that a chemical substance is a natural constituent of living tissues has always led to an increase in experimental work in that field, and for 16 years heparin was regarded as the chief product of the mast cell. Then, after both heparin and histamine had been shown to be simultaneously released from dog liver following anaphylactic shock, it was found that most of the body histamine also originates from the mast cell. Following lethal doses of fluorescent histamine liberators, Riley and West (1953) found that the fluorescent material was sharply localised to the mast cells which thereafter broke up and released histamine. Analysis then showed that there is a good correlation between the mast-cell count of a particular tissue and the amount of histamine that can be extracted from it.

However it seems that the production of heparin and histamine are but part of the function of the mast cell, since these cells are plentiful in lower organisms which lack a blood-vascular system. Even in higher animals, the mast cells appear to be associated with the tissues rather than with the blood vessels. There are other functions which are probably fundamental between

mast cells and connective tissue, and more work along these lines is clearly indicated. For example, Asboe-Hansen in 1954 reported a parallelism between the mast-cell count and the hyaluronic-acid content of many normal and pathological tissues. He has in fact proposed that mast cells under varying hormonal influences secrete hyaluronic acid, perhaps by way of a heparin precursor. And Benditt and his co-workers showed in 1955 that mast cells in peritoneal washings from the rat contain 5-hydroxytryptamine. Whatever other materials remain to be discovered in mast cells, it is certain that they are the site of active metabolic processes, since several enzymes can be detected in homogenates of cell concentrates.

I propose to deal with the constituents I have mentioned and to touch on the evidence upon which each conclusion has been reached ; then, after indicating certain difficulties or exceptions, I shall attempt to give our views on the biological significance of mast cells.

Heparin.—Swedish workers have been traditionally interested in anticoagulants and credit goes to Jorpes and his colleagues for having traced the source of tissue heparin. Heparin is the only naturally occurring mucopolysaccharide with strong anticoagulant action. As we now know, it is a polymer of disaccharide units each containing glucuronic acid and an amino-sugar, glucosamine. The amino-sugar in heparin is sulphated and it is the sulphate moiety which confers on the heparin molecule its anticoagulant property. The theory that mast cells produce heparin is based on three facts—(i) the metachromatism of the granules, (ii) heparin can be extracted from tissues rich in mast cells, and (iii) the heparin content of a tissue is a guide to its mast-cell population (Fig. 1). Recently mast-cell granules have been isolated from mouse connective tissue and shown to possess powerful anticoagulant properties characteristic of heparin. Another significant function of heparin may be chylomicron dissolution whereby the passage of neutral fat through the capillary walls is facilitated. This clearing factor may be a heparin-activated lipoprotein. The concentration of heparin needed for this use in fat transport is considerably less than that necessary for inhibiting the blood clotting system.

Histamine.—Histamine is derived from histidine by simple decarboxylation. Several workers have reported that histidine decarboxylase is in mast cells, and recent work indicates that these cells take up the amino-acid but not the amine. Radioactive histidine when injected can be found in the region of mast cells as radioactive histamine, but radioactive histamine when injected is not similarly concentrated.

As with heparin, we have found a good correlation between the histamine content of a particular tissue and the number of mast cells it contains (Fig. 2). Even within one species, there is an association between the mast cells of various areas and the histamine values, though the amount each cell carries varies according to the maturity of the cell, the type of heparin, and the extent of

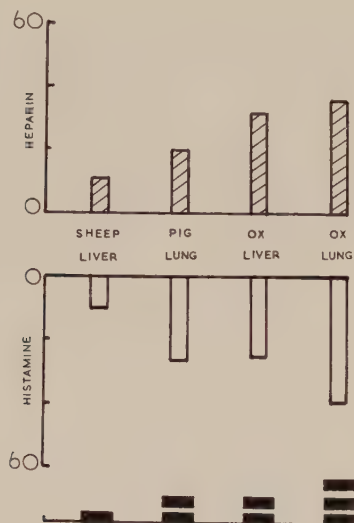


FIG. 1.—The relationship between the heparin content (i.u./g.), histamine content ($\mu\text{g./g.}$) and relative mast-cell count (lower shaded blocks) of four tissues.

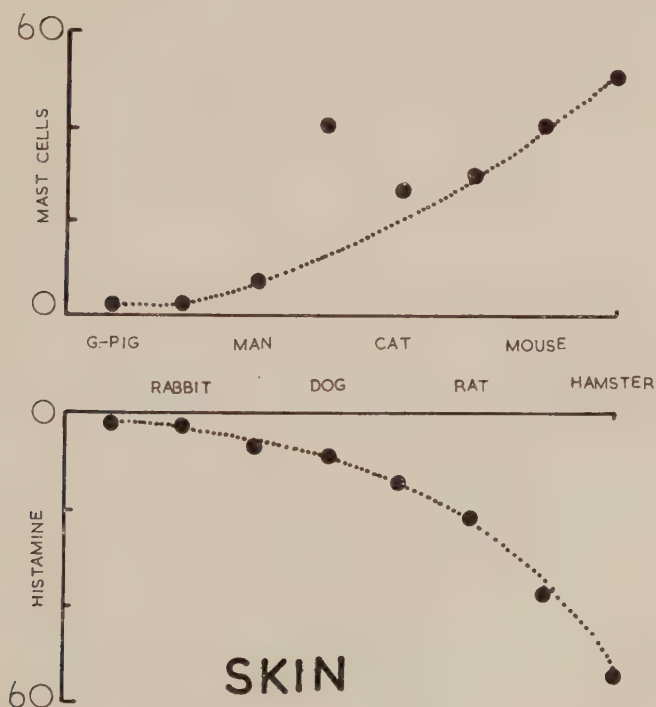


FIG. 2.—The relationship between the mast-cell count (cells per H.P. field) and the histamine content ($\mu\text{g./g.}$) of the skin of several species.

degranulation. As mast cells form and increase in number, so the histamine content of that particular tissue rises. Mention must be made, however, of the fact that mast cells in different species do not always react similarly to damaging agents. For example, it is easy to show that certain histamine liberators completely disrupt mast cells in the rat but have little action on similarly-located cells in the guinea-pig, mouse or hamster.

When pathological tissues rich in mast cells are examined, extremely high values for histamine and heparin may be found. The common mast-cell lesion in man (urticaria pigmentosa) contains more histamine and heparin than is present in the adjacent skin and lightly stroking these lesions rapidly produces a reactive wheal limited to the lesion itself and probably the result of released histamine. Occasionally, the lesion presents as a solitary tumour-like nodule and we have had the opportunity of examining two such nodules. Such tumours however are relatively common in dogs where lymph nodes in the dermis are usually involved. Mr. Head of Edinburgh has very kindly supplied us with over 50 from dogs, 2 from cats and 2 from cows (Figs. 3, 4 and 5). Present

Amine Content of Mast Cell Tumours
($\mu\text{g/g}$)

Species	Histamine	5-HT
MAN (2)	233 (8)	<0.05
DOG (6)	788 (23)	<0.04
COW (2)	150 (19)	<0.03

FIG. 3.—Comparison of the histamine content ($\mu\text{g./g.}$) and 5-HT content ($\mu\text{g./g.}$) of mast-cell tumours of several species. Numbers in parentheses represent number of specimens and the amine content of normal skin of these species. Note that the 5-HT contents are insignificant.

evidence suggests that histamine is located in the mast-cell granule, and when the granules disappear (as they do in injury) the histamine is released. Since histamine and heparin carry opposite charges chemically, it might be assumed that they co-exist in the granules in the form of a salt—the heparinate of histamine. But this simple explanation is not entirely satisfactory and further work is necessary to elucidate the linkages involved.

Hyaluronic acid.—This is a high polymer composed of equimolecular quantities of acetyl-glucosamine and glycuronic acid residues joined by β -glycosidic links. It differs from heparin chiefly in being sulphate-free. It is one of the

best characterized of the extra-cellular substances of the connective tissues, being a component of the ground substance which partly supports capillary walls and acts as a barrier to the free passage of materials to and from the capillaries, tissue cells and environment. The methods available for the identification of hyaluronic acid in tissues include staining first of the tissue polysaccharides, then of the acid polysaccharides, metachromatic staining with toluidine

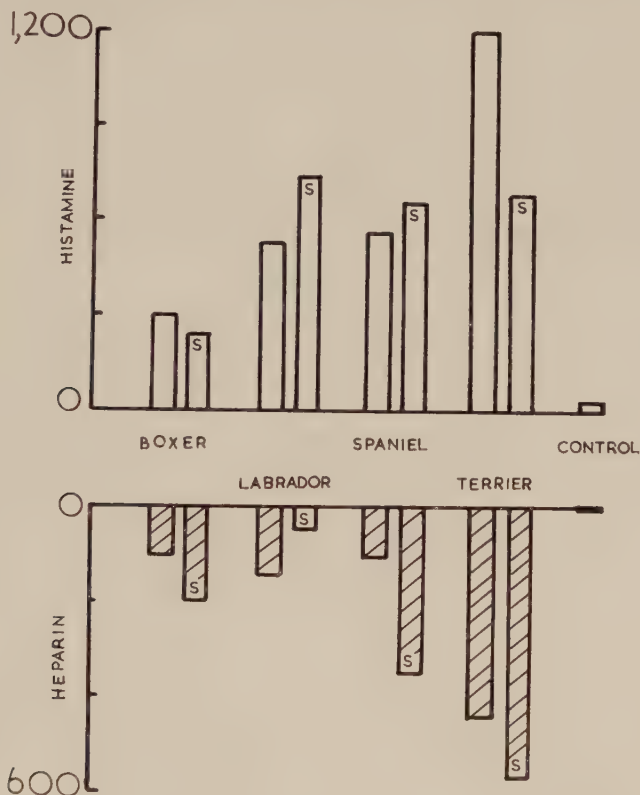


FIG. 4.—Comparison of the histamine content ($\mu\text{g./g.}$) and the heparin content (i.u./g.) of four dog mast-cell tumours. After excision, these recurred and the values then obtained are shown in the histograms marked S.

blue, and digestion by the specific enzyme hyaluronidase. Asboe-Hansen is convinced that Ehrlich's mast cells secrete the mesenchymal mucinous substance, hyaluronic acid.

5-Hydroxytryptamine (5-HT).—This amine is derived from 5-hydroxytryptophan which in turn is formed from tryptophane. The distribution of 5-hydroxytryptophan decarboxylase has been well studied and results suggest that it is not concentrated in tissues rich in mast cells.

We have carried out extensive studies on many species and have found no

correlation between 5-HT and mast cells (Fig. 6). Only in the rat and mouse is much 5-HT contained in the skin, and even in these two species we now have the means of releasing one amine leaving the other almost untouched or at the most down to 80% of its initial value. Nevertheless, Benditt and his co-workers believe that much 5-HT is contained in the mast cells, particularly in the rat.

Passing to the pathological tissues, mast-cell lesions of the dog, cat, cow and man have all failed to give raised 5-HT values although the tissue histamine has been exceptionally high (Table I). Certain other substances may be extracted

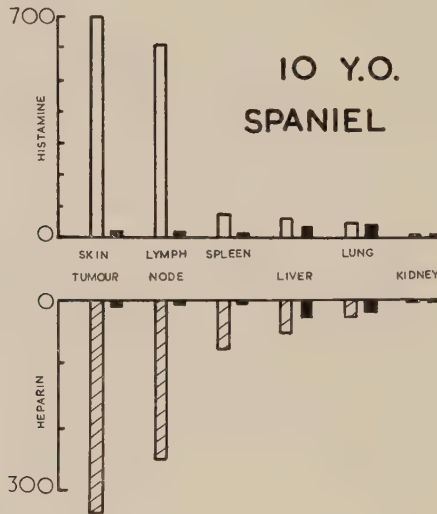


FIG. 5.—Comparison of the histamine content ($\mu\text{g./g.}$) and the heparin content (i.u./g.) of tissues of a dog with a mast-cell tumour. Control values for the tissues are shown as shaded histograms. Note that metastases in the lymph node, spleen and liver have produced raised histamine and heparin values.

TABLE I.—Comparison of the Mast-cell Count (cells per H.P. field), Histamine Content ($\mu\text{g./g.}$) and 5-HT content ($\mu\text{g./g.}$) of Tissues of a Dog and a Cat, each having a Mast-cell Tumour in the Inguinal Skin Region. Numbers in parentheses are the values of tissues from normal animals. Note that the cat spleen contains large numbers of mast cells and much histamine. The 5-HT values in both species do not exceed the normal levels.

Tissue	6-year-old Spaniel			3-year-old Cat		
	Mast cells	Histamine	5-HT	Mast cells	Histamine	5-HT
Inguinal skin tumour .	112 (5)	800 (9)	0.03	42 (4)	80 (24)	0.03
Lymph node	58 (2)	200 (4)	0.03	33 (2)	285 (11)	0.03
Spleen	27 (2)	150 (5)	1.16	81 (1)	1,230 (2)	1.20
Liver	14 (10)	100 (25)	0.22	56 (8)	14 (1)	0.08

from these lesions but they do not possess all the properties of 5-HT. When dogs are subjected to anaphylactic shock or to histamine liberators, histamine and heparin are released from the liver cells into the thoracic duct and hepatic vein with mast-cell disruption but no 5-HT release occurs although dog liver contains relatively much 5-HT. We come to the conclusion that little 5-HT is contained in mast cells of the dog.



FIG. 6.—Comparison of the mast-cell count (cells per H.P. field), histamine content ($\mu\text{g./g.}$) and 5-HT content ($\mu\text{g./g.}$) of the skin of various species. Note that only rat and mouse contain much 5-HT.

Difficulties.—Interest tends to become focussed nowadays on possible exceptions to the rule that heparin and the bulk of histamine in a tissue are normally contained in mast cells. One such unusual location for histamine is in the mucosa of the pyloric portion of the stomach of many species. Here some cell other than the mast cell must be binding the histamine since mast cells are scarce in layers where the histamine content is very high. The obvious choice is the mucin of the goblet cells. These cells are resistant to the action of histamine liberators and very little histamine is released from this area of the gut under such treatment.

Eosinophils used to be considered the chief source of histamine, but recently the relationship of eosinophils to histamine has been less close. Eosinophils are found in mast-cell lesions when the mast cells are in the process of disruption. They appear, for example, when lesions of urticaria pigmentosa are irritated or when dog tumours are treated with histamine liberators. Perhaps the eosinophil is more concerned with detoxification and disposal of histamine than with its elaboration. The basophil or blood mast cell always carries histamine and thus resembles the tissue mast cell.

Objections to the theory that mast cells secrete hyaluronic acid are based on the facts that hyaluronidase does not destroy the metachromasia of mast-cell granules and that there is sometimes a poor correlation between the mast-cell count and the hyaluronic acid content of a tissue. For example, mast-cell tumours and organ capsules exceptionally rich in mast cells contain little ground substance, and conversely embryonic tissue rich in ground substance has few mast cells.

Significance of mast cells.—Histologists long ago suggested that the function of the mast cells was concerned in some way with connective tissue and particularly with the formation of fibrils. The formation of the first mast cells in the embryo is always preceded by general metachromatism of the tissues. Thereafter tissue mast cells undergo cyclic changes, disappearing in areas of acute tissue injury and reappearing when connective tissue fibrils begin to be laid down. This behaviour suggests that mast cells alternately form, store and release certain substances. Such a release is followed by activation of the reticulo-endothelial system and flooding of the tissue with protein-rich oedema fluid, formed as a result of the increased vascular permeability by histamine and possibly by 5-HT also. Of the species so far studied, however, only in the rat is 5-HT more active than histamine in increasing capillary permeability and only in the rat is 5-HT present in the skin in substantial amounts. It is unlikely that these two factors are coincidental. Neither can it be by chance that the only species developing the full anaphylactoid reaction is the one which contains much 5-HT in its skin.

The question arises why human mast cells do not concentrate 5-HT. It is possible that this amine is too toxic to the sensory organs in the skin for it to remain there. It is already known, for example, that the pain-producing threshold concentration of 5-HT when applied to human skin as at the base of a blister is very low, of the order of 1 part in 1,000 million.

The function of histamine and 5-HT in tissues thus remains an enigma. Many facts suggest that histamine is concerned with the defence of the body since its release is followed by a temporary mobilization of the loose mesenchyme. It is remarkable that in all species except the rat histamine and mast cells are concentrated in the outer layers of the skin—cell layers which come into contact with the outside world. In the rat, 5-HT is concentrated in this region and may

take over part of the defence function of histamine. I believe that mast cells act as part of the defence mechanism of the body whereby they react quickly to any kind of cell injury. The local action of the released amines results in the formation of oedema fluid, which assists in the removal of foreign materials and floods the tissues with protein-rich fluid ready for the job of repair.

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URTICARIA PIGMENTOSA AND ALLIED DISORDERS.

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URTICARIA PIGMENTOSA has always been a favourite subject with dermatologists. The condition was first described in 1869 by Nettleship and independently six years later by Tilbury Fox (1875). It was named by Sangster in 1878 and its association with Ehrlich's mast cell demonstrated in 1887 by Unna. The studies of Graham Little in 1905-06 and of Finnerud in 1923 established most of the clinical features of the condition and Hannay in 1925 demonstrated convincingly that there was no real difference between the adult and infantile varieties.

The essential clinical features of the condition are fairly constant. Nodular lesions are more common in babies but can occur in adults and macular lesions are more often found in adults but are not uncommon in young children. Bullous lesions are almost confined to infants, possibly because large collections of mast cells are more often seen in babies but more likely because the infantile skin is thin and blisters readily, just as it does in impetigo and papular urticaria of the very young child. Telangiectasia macularis eruptiva perstans as described by Parkes Weber (1930) is now accepted as a clinical variant of urticaria pigmentosa. Verrucous lesions have been seen by Goldsmith and Wells (1951) and a rare papular form consisting of confluent papules 1-3 mm. in diameter covering the entire body surface, except the face, and tending to resemble xanthomata in the axillae and groins has been described three times (Graham *et al.*, 1942). Cases without pigmentation have been seen but since pigmentation is probably secondary to the biochemical activity of the underlying mast-cell infiltrate, and possibly also dependent on the depth of the infiltrate in the dermis, this is of little importance.

All these one would regard as simple clinical variants of the condition which we know as urticaria pigmentosa but solitary lesions (Chargin and Sachs, 1954; Drennan and Beare, 1954) are in many ways so different that I think they should be classified separately. These localized collections of mast cells are almost certainly of naevoid origin. The cutaneous diffuse mastocytosis described by Degos (1955) is another mast-cell disorder which has special features sufficient to distinguish it from urticaria pigmentosa. The skin here has a yellowish thickened appearance, is of a doughy consistency or smooth and scattered with tiny elevations giving it a leathery appearance (Degos, 1953). Cutaneous folds are exaggerated. This change is first marked in the axillae

and groins and in extreme examples of the disorder the skin is pachydermatous. Nodules, bullae and small dermal tumours may also be present. Pruritus is intense. Histologically—as one would expect—there is a diffuse infiltration of mast cells.

Twenty-two cases seen in a ten-year period have included one patient with bullous reactions and associated generalized flushing, one with non-pigmented lesions, one with suspected systemic lesions (see below) and four with solitary mast-cell naevi.

Urticaria pigmentosa without mast cells.—One is inclined to-day to view with suspicion cases of otherwise typical urticaria pigmentosa in which mast cells are not found histologically. One requires close co-operation and understanding between clinician and pathologist or else a measure of good luck to get a positive biopsy—for three reasons: First, mast cells become hydrated to bursting point within a few minutes of exposure to an isotonic solution, such as the oedema fluid of urtication (Drennan, 1951). The mast-cell granules, composed of mucopolysaccharides, rupture the cell by their ability as hydrophilic colloids to absorb water and increase rapidly in bulk (Day, 1949). With the rapid change in form and with loss of heparin granules and consequently loss of specific metachromatic staining, these cells can readily be mistaken for lymphocytes, plasma cells, fibroblasts or “just mononuclears” (Drennan, 1951). Thus, the handling of the lesion during the biopsy or the injection of local anaesthetic too close to the lesion may make the specimen useless. Second, in many cases, particularly of the solitary mast-cell naevus type, the bulk of the lesion may be found to consist of very primitive mast cells and the histological section obtained may consist only of this area. These primitive cells contain few or no heparin granules. Third, heparin granules are water soluble. The biopsy specimen should therefore be fixed in an alcohol fixative and the pathologist must be asked specifically to look for mast cells.

Pharmacology.

The dermatographism, localized urtication and tendency to develop bullae which are so readily explicable on the theory of histamine liberation (Riley and West, 1952) are not controlled to any appreciable extent by antihistamine drugs, but the alarming generalized flushing, tachycardia, which are occasionally found (Marten, 1957, and in a case of my own) are greatly helped by maintenance antihistamine therapy. Cortisone in high dosage seems to have little or no effect in controlling symptoms.

Systemic Lesions.

The older literature contains reports of lymph—node enlargement (e.g., Gray, 1938), and also occasional mention of various blood disturbances

including prolongation of the coagulation time and bleeding time. Touraine *et al.* (1933) recorded urticaria pigmentosa in a man of 55 with splenomegaly and a lymphoid and myeloid reaction in the peripheral blood, and Bertelotti (1943) a similar case—urticaria pigmentosa in a man aged 49 with splenomegaly and mast-cell hyperplasia of bone marrow and lymph glands. However, the possible potentialities of the mast cell were really first emphasized by Bloom, a veterinary pathologist, who in 1942 described mast-cell tumours in dogs. He found both solitary and multiple tumours and he regarded the latter as malignant. Ellis reported a remarkable case in 1949: A one-year-old child with a history of urticaria pigmentosa from birth died of gastroenteritis. At autopsy there was mast-cell infiltration of spleen and liver (with cirrhosis) and of kidneys, lymph nodes, bone marrow, peri-adrenal fat and interstitial tissues of the pancreas. There followed in 1952 a report by Sagher *et al.* of concomitant bone changes in urticaria pigmentosa and in 1956 Sagher and Schorr gave their report from a Central Registry which they had set up to correlate skeletal x-ray changes found in cases of this disease. Nineteen of 55 patients examined radiologically had demonstrable bone changes. There were two distinct types of bone lesion:

(a) A localized type (found in 15 patients including three children) showing calcified deposits and decalcified areas of various size in humerus, radius, femur, skull and shoulder.

(b) A generalized type (found in four adult patients) with generalized cystic osteoporosis of the ribs with thickening of bony trabeculae, stippling of the bony structure of the skull and thickening of the skull tables, and generalized sclerosis of pelvic bones and vertebrae. This is a bony pattern consistent predominantly with osteosclerosis.

It has been shown (Drennan and Beare, 1954) that primitive mast cells have phagocytic and reticulin-forming properties which suggest that mast cells have a common ancestry with tissue macrophages and reticulum cells. Modern opinion favours the view that tissue mast cells develop from undifferentiated precursors in the perivascular mesenchyme. Drennan (personal communication, 1957) believes that mast cells must be closely related to fibroblasts (common spindle form, mucopolysaccharide nature of secretion, tendency for immature forms to grow in a network with interconnected cell processes). If this is so it is not difficult to imagine mast cells arising from bone marrow reticulum reverting to fibroblast form, and the tendency for myeloid hyperplasia to result in fibrosis might well be accentuated if the cell type in demand was the mast cell. So might one explain the osteosclerosis of systemic urticaria pigmentosa.

All the available evidence at the present suggests that the bone changes seen in urticaria pigmentosa are due to infiltration with mast cells and the associated sclerosis, and there are now a sufficient number of published case

reports to provide some idea of what one may occasionally expect in urticaria pigmentosa in the event of systemic change taking place. We do not yet know how frequently this change is likely to be found but probably the original view that urticaria pigmentosa is essentially a benign eruption eventually clearing spontaneously remains true. Nevertheless, very serious systemic changes are possible.

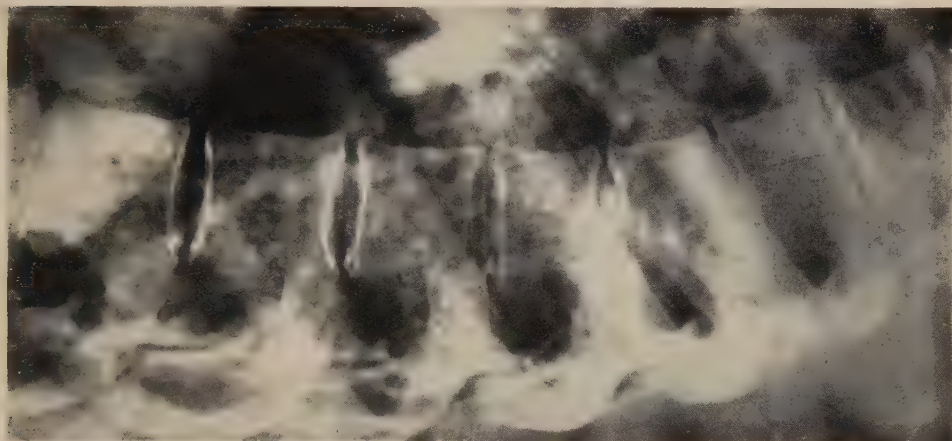


FIG. 1.

Among 11 cases of my own which I reviewed recently bone changes were found in one. This was a 28-year-old girl with a history of urticaria pigmentosa of macular type for ten years. Skiagrams revealed rarefaction without sclerosis of the twelve thoracic vertebrae (Fig. 1). All other bones and all other clinical and laboratory investigations were normal. In the absence of any contrary evidence one must presume that the changes in the thoracic spine are due to mast-cell infiltration. The patient did not complain of any symptoms referable to the spine.

Examples of minor bone change recorded in the literature are set out in Table I.

Drs. Tomlinson and Feiwei kindly showed me a skiagram of a case which they had studied where mast-cell infiltration had led to collapse of the 11th dorsal vertebra; these bony infiltrations may present great diagnostic difficulties, especially when the possibility of systemic mast-cell disease is not appreciated.

Moderately serious mast-cell disease is represented in the cases listed in Table II and in these patients hepatosplenomegaly is a prominent sign. Not all cases recorded here had x-ray examination of the whole skeleton.

TABLE I.—*Minor Bone Changes in Association with Urticaria Pigmentosa.*

<i>Children.</i>	
Clyman and Rein (1952)	Mottled calcified deposits in upper third of humeri, and upper third of femora; slight sclerosis of medullary cavities of upper third of tibiae.
Grupper (1954)	Two decalcified areas at the distal part of the right femur near the metaphysis.
Shair and Casper (1955)	Both radial shafts showed irregular contours with cortex alternatively thinner and thicker than normal.
Edelstein (1956)	Periosteal thickening of long bones.

<i>Adults.</i>	
Stark, Van Buskirk and Daly (1956)	Male aged 54. Patchy decrease in bone density with coarsening of trabeculation particularly involving metaphyses of long bones and lumbar vertebrae. Bone biopsy showed mast-cell infiltration.
Calnan (1953)	(a) Female aged 24. Clear-cut annular deficiency 1 cm. diameter with sclerosed margins in left parieto-frontal region of skull. (b) Female aged 52. Small ill-defined defect 5 mm. in diameter in right frontal bone.
Deutsch, Ellegast and Nosko (1956)	Male aged 50. Localized osteosclerosis in second lumbar vertebra and in pelvis. Mast cells in bone marrow.

TABLE II.—*Moderately Severe Mast-cell Disease.*

Rider, Stein and Abbuhl (1957)	Aged 2½. Urticaria pigmentosa since birth, anaemia, hepatosplenomegaly. Irregular widening of skull and large bones with loss of normal contours. Metacarpals and phalanges irregular in size and shape. Mast cells on liver biopsy.
Zak, Covey and Snodgrass (1957)	Female aged 58. Long-standing urticaria pigmentosa. Hepatosplenomegaly. Abnormal areas of variable density in spine, ribs and pelvis. Mast-cell infiltration of iliac marrow (bone biopsy).
Bluefarb and Salk (1954)	Male aged 30. Telangiectatic type of urticaria pigmentosa. Gastroenteritis for many years. Splenomegaly. Cystic osteosclerosis of ribs, vertebrae and clavicles.
Asboe-Hansen and Kaalund-Jørgensen (1956)	Male aged 35. Urticaria pigmentosa. Hepatomegaly. Mast-cell infiltration in liver biopsy. Increase in granulated basophils in sternal marrow (4·7–10·3%). Numerous mast cells or basophils in bone biopsy. 3·0–9·5% basophils and 2·0–7·5% monocytes in the peripheral blood.
Touraine, Solente and Renault (1933)	Male aged 55. Urticaria pigmentosa since infancy. Splenomegaly. Lymphoid and myeloid reaction in peripheral blood.
Bertelotti (1943)	Male aged 49. Urticaria pigmentosa for six years. Splenomegaly. Hyperplasia of mast cells in bone marrow and lymph glands.
Degos, Lortat-Jacob, Hewitt and Ossipowski (1952)	Male aged 56. Pigmented nodules and extensive erythematous infiltration of skin. Hepatosplenomegaly. Lymphadenopathy.

Serious mast-cell disease is summarized in Table III and in most of these patients bone marrow replacement symptoms are noticeable.

Death from some form of leukaemia associated with mast-cell disease occurred in the three cases mentioned in Table IV.

It is important to consider the differences between the tissue mast cell and the blood basophil, because on this differentiation rests the terminology which

TABLE III.—*Serious Mast-cell Disease.**Children.*

Ellis (1949)	One year old. Urticaria pigmentosa since birth. Mast-cell infiltration of spleen and liver with cirrhosis, kidneys, lymph nodes, bone marrow, periadrenal fat, interstitial tissues of pancreas. Gastroenteritis. Cachexia. Death.
Brodeur and Gardiner (1956)	Aged 5. Urticaria pigmentosa from age of two months. Excessive bleeding after trauma from age of 2. At age 5, hepatosplenomegaly, retarded growth, chronic ill-health. Mast cells in bone marrow, lymph nodes and peripheral blood.

Adults.

Reilly, Shintani and Goodman (1955)	Male aged 34. Severe gastroenteritis and urticaria pigmentosa for many years. Hepatosplenomegaly. Mast-cell infiltration and periportal fibrosis of liver. Mast-cell infiltration of sternal and rib marrow. Anaemia, granulocytopenia. Osteoporosis and pagetoid thickening of bony trabeculae in skull, pelvis, ribs and humeri.
Berlin (1955)	Male aged 71. Urticaria pigmentosa of few months' duration. Mucous membrane involvement. Gastroenteritis for 20 years. Hepatosplenomegaly. Thirty-five per cent. mast cells in sternal marrow. Leukopenia. Thrombocytopenia. Bleeding on slight trauma.
Hissard, Moncourier and Jaquet (1951)	Male aged 50. Paroxysms of itching, tachycardia precordial pain and swelling of skin. Skin: Erythema, pachydermia, nodules and tumours, haemorrhage on slight trauma; no pigmentation. Hepatosplenomegaly. Mast-cell infiltration of sternal marrow and spleen. Fifteen per cent. mast cells in peripheral blood after injection of epinephrine and 45% after splenic puncture. Consistent monocytosis in blood (up to 20%).

TABLE IV.—*Death from "Leukaemia".*

Waters and Lason (1957)	Aged 5. Generalized rash. Lymphadenopathy. Mast cells in peripheral blood and sternal marrow. At autopsy: Mast-cell invasion of skin, liver, spleen, lymph nodes, bone marrow and perivascular connective tissue of epicardium and of submucosa of small and large intestine. Interpreted as "mast-cell leukaemia".
Sagher, Libani, Ungar and Schorr (1956)	Female aged 55. Urticaria pigmentosa for five years. Hepatosplenomegaly. Enlargement of all superficial lymph nodes. Osteosclerosis of all bones. Death from monocytic leukaemia.
Efrati, Klajman and Spitz (1957) (autopsy)	Female aged 52. Urticaria pigmentosa without pigmentation. Hepatosplenomegaly. Focal osteosclerosis in vertebrae. Leucocytosis 62,000 (22-76% mast cells—many immature). Bone marrow showed 18-26% mast cells. At autopsy: Mast cells in liver and spleen. Interpreted as "mast-cell leukaemia".

can properly be used to describe some of the cases in the last group. Waters and Lason (1957) compare the two cells and point out that the only common characteristic is metachromasia of the granules and an associated content of heparin and histamine. The tissue mast cell has a round or oval nucleus, rarely indented and may have wide variation in cytoplasmic contours. The granules vary from fine to coarse and may obliterate the nucleus. By contrast the blood basophils usually have a small cell body with a polymorphous or

lobulated nucleus, and the granules tend to be more irregularly distributed. Their origin is presumably in bone marrow and they exist as a normal constituent of peripheral blood.

In the case described by Waters and Lacson, a child aged five years, tissue mast cells were demonstrated in the peripheral blood and there was generalized infiltration of the body organs with these cells. In the case described by Efrati *et al.* (1957) immature tissue mast cells in enormous quantities were found in the peripheral blood. There was also an increase in circulating eosinophils and it is of incidental interest to note that systemic cortisone produced a temporary reduction in both the mast-cell and eosinophil counts. Both these cases have therefore been classified by their authors as mast-cell leukaemias. As far as I know, however, only the case recorded by Efrati *et al.* had demonstrable circulating immature tissue mast cells.

One notes the frequent mention of gastroenteritis in these severe mast-cell syndromes. It seems possible that this might be due to production of serotonin or histamine by mast-cell infiltrates.

We are left, I think with the distinct impression that urticaria pigmentosa may not always be a benign dermatosis and though there are many reasons why we might regard some of the syndromes as malignant disease of the reticulo-endothelium system, the evidence is as yet incomplete for a satisfactory classification.

I wish to thank Dr. Ivan H. McCaw for referring cases of urticaria pigmentosa for this study, Drs. J. M. Drennan and J. B. Gibson for help on matters relating to the pathology of mast-cell disease, Dr. W. H. T. Sheperd for advice on the interpretation of skiagrams and Mr. R. Wood for preparing Fig. 1.

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ROYAL SOCIETY OF MEDICINE.

SECTION OF DERMATOLOGY.

President—Dr. JOHN T. INGRAM.

20 March 1958.

A symposium on mast cell disorders was held, with opening papers as follows :

Cutaneous Mast-Cell Tumours in the Dog, Cat and Ox.—Mr. K. W. Head.

Pharmacology of the Tissue Mast Cell.—Dr. G. B. West.

Urticaria Pigmentosa and Allied Disorders.—Dr. J. Martin Beare.

These papers are published on earlier pages in this journal.

Urticaria Pigmentosa in Identical Twins.—Dr. W. FRAIN-BELL (for Dr. R. T. BRAIN).

Twin girls aged $4\frac{1}{2}$ years.

History.—At the age of 5 months, both girls developed brown macules. In one twin they first appeared on the buttocks and in the other, on the outer aspects of the upper thighs. One child produced lesions 10 days before the other. In both they spread very gradually, mostly on the trunk, until the age of 2 years. Since then there have been no fresh ones. None of the lesions has disappeared and they have remained macular in type. Both children develop urtication on friction. Their general health has been normal, except for a generalised rash immediately following vaccination 2 weeks before the onset of the urticaria pigmentosa. They were born 8 weeks prematurely. No other member of the family has been similarly affected.

Examination.—Widespread pigmented macules ; urtication is present on friction. The lesions are distributed mainly on the trunk and one twin has a greater number, especially on the buttocks. Routine physical examination showed no abnormality. It has not been possible to carry out a satisfactory X-ray examination.

E. Stroud and M. H. Lees (1958) have recently followed up 45 cases of urticaria pigmentosa in children seen at Great Ormond Street in the last 10 years. They were able to trace 32 cases, and in 6 of these, systemic abnormalities were discovered. Apart from osteoporosis, they were heterogeneous.

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Mastocytoma (Mast-Cell Naevus).—Dr. MICHAEL FEIWEL and Dr. JOHN EVERALL.

A girl aged 4 years.

History.—A persistent solitary macule on the back of the trunk since birth. On occasions, bullae have developed over the lesion. An only child. General health satisfactory. No relevant family history.

Examination.—A solitary, brown, raised lesion on left lower thoracic region measuring 2 by 2.5 cm. Erythematous flare and urtication occur after rubbing the lesion. Abdominal palpation reveals no abnormality. No lymphadenopathy.

Urticaria Pigmentosa with Attacks of Flushing.—Dr. A. HERXHEIMER (for Dr. H. J. WALLACE.)

History.—This man, aged 49, has had widespread urticaria pigmentosa as long as he can remember.

Since 1947, he has had attacks of flushing of the skin, headache and nasal obstruction. The flush, which may be accompanied by feeling faint, is most intense on the face, less on the trunk and arms, and least on the legs. The body temperature may be raised during the attack to 101–102° F. Towards the end of the attack, he sometimes feels nausea; vomiting has occurred on four occasions. In some attacks there is an urge to defaecate, but no pain. In a few attacks he has lost consciousness and he has twice been incontinent of urine. The skin lesions show no change during an attack.

The attacks, which last about half an hour, occur at irregular intervals, singly, or in twos and threes within a few days. Between these bouts he is free for 1–8 weeks (average 2 weeks).

Attacks are not brought on by alcohol or aspirin, by baths or skin friction and no precipitating factors have been discovered.

Examination.—Urticaria pigmentosa of trunk and upper parts of limbs. Also pigmented lesions on the hard palate. No abnormality was found in the nose or the retropharyngeal space (Mr. Carruthers).

Investigation.—While the patient was in hospital, an attack of flushing was observed. About fifteen minutes after the onset, the skin was flushed and warm all over the body except for the soles of the feet. The blood pressure had fallen from the normal 120/80 to 72/24: the patient had a headache and his nose was blocked. Plasma taken about thirty minutes after the onset of the attack, when it was subsiding, did not contain increased amounts of histamine (Dr. R. S. Stacey), nor was any abnormal anticoagulant activity found (Dr. G. I. C. Ingram). Dr. Stacey also found that no more histamine appeared in the urine during the period that included the attack than during a control period (57 and 56 $\mu\text{g.}^*$ hr. respectively), and that the plasma histaminase was normal: the Sjoerdsma-Udenfriend test for excess urinary 5-hydroxy-indole-acetic acid was negative.

On another day, an intravenous infusion of 32 $\mu\text{g.}^*$ histamine acid phosphate per minute for six minutes produced a fairly intense flush of the face and a mild one elsewhere, together with a slight headache. The severity was not increased by further discontinuous doses totalling 330 $\mu\text{g.}^*$ given during the following eighteen minutes, but at the end of this period the patient felt very tremulous; he had noticed the same feeling after severe spontaneous attacks.

X-rays of the skull show multiple small translucencies scattered over the vault. The appearance has not changed between 1954 and 1957. The pelvis, spine and ribs do not show such translucencies.

Haemoglobin 95%, W.B.C. 7,100, normal differential count. Plasma proteins, total 8.7 g./100 ml. (albumin 5.2 g./100 ml., globulin 3.5 g./100 ml.): serum electrophoresis showed increased β - and γ -globulins. Gastric acid secretion in response to histamine normal. Electroencephalogram normal.

Comment.—The symptomatology of the attacks is most readily explained by supposing that histamine is responsible. The fact that no increase was found in the plasma or urinary histamine might be due to very rapid inactivation of histamine, which is known to occur in some animals. Some of the symptoms, such as nasal congestion and nausea, were not reproduced by the infusion of histamine but this could be due to differences in dose and route of administration. The absence of any visible change in the skin lesions seems to indicate that these are not the source of histamine or other substances that may be released during the attacks.

When the patient was first seen, he thought that attacks could be precipitated by alcohol, but this could not be convincingly demonstrated. On two occasions in hospital,

* Expressed in terms of the base.

an attack occurred $2\frac{1}{2}$ hours and 4 hours respectively after the ingestion of alcohol, but on several other occasions no attack followed.

The periodicity of the attacks is striking. Careful records kept by the patient over the past 15 months show that the interval between successive attacks is either short, two days or less, or longer than six days, suggesting that there is a refractory period. This might correspond to the period that is required for mast cells to become recharged after their contents have been released.

DISCUSSION.

THE PRESIDENT: This is very like the reaction to carcinoid with secondaries and there is a relationship between the two conditions.

DR. A. HERXHEIMER: I did not stress the difference between this condition and carcinoid; the carcinoid patient usually develops a variegated pattern made up of red, blue and white areas, and the skin is cool. This man was bright pink all over and his skin was warm and that is just what happens when histamine is infused.

DR. G. B. WEST: The flushing seen in patients with urticaria pigmentosa is reported to be controlled by treatment with reserpine. Since reserpine lowers the tissue 5-HT, such a result suggests that 5-HT, not histamine, is involved in the flushing syndrome. Although the blood level of 5-HT is not dramatically raised by reserpine, this does not preclude a raised local concentration of 5-HT sufficient possibly to account for the flushing and stuffy nose sometimes seen in patients with urticaria pigmentosa.

DR. MARTIN BEARE: With one of our child patients we noticed that every time the child had generalized flushing, one or more of the lesions became bullous. There was no constant time factor, but travelling always brought on an attack of flushing.

DR. M. FEIWEL: In a recent paper (Bloom *et al.*, 1958) the patient, a child with urticaria pigmentosa, also suffered from attacks of flushing and unconsciousness. These attacks ceased when two tumours of urticaria pigmentosa were surgically excised.

REFERENCE.

BLOOM, G., DUNÉR, H., PERNOW, B., WINBERG, J. and ZETTERSTRÖM, R. (1958) *Acta Paediat. (Stockh.)*, **47**, 152.

Multiple Pyogenic Granulomata.—Dr. W. FRAIN-BELL.

A male accountant aged 56.

History.—Three months ago, this patient developed a dusky bluish swelling over the bridge of the nose, soon followed by two small bright red papules. He punctured these two lesions which bled freely. Gradually over the next six weeks, numerous similarly coloured papules appeared. There have been no fresh lesions for the last six weeks. During the last three weeks, a few of them have become smaller, while others appear to be harder in consistency.

Examination.—Over the bridge of the nose there are bright red papules of various sizes (Fig. 1); the colour disappears on pressure in most instances.

Histology.—(Dr. H. Haber). In the dermis there are masses of cells showing vasoformative properties. There is no inflammatory reaction or oedema.

Comment.—Multiple pyogenic granulomata appear to be a distinct clinical entity. The initial lesion is identical in appearance with a type of pyogenic granuloma with a smooth shiny surface like a small red cherry. In most instances, the primary tumour is exposed to trauma, such as surgical excision, curettage, cauterisation or diathermy. This is followed, after a variable interval, by the production of satellite lesions around the primary site. The fresh ones vary in size but are otherwise morphologically similar to the primary lesion, although they may be darker in colour. The condition has been previously reported only in young people between the age of 8 and 16 years (Foldvari, 1935; Sims *et al.*, 1948; Canter, 1949; Evans, 1954; Evans and Warin, 1957). Evans (1954) described the case of an 8-year-old boy, in whom the primary red papule on the back was excised, but a month later satellite lesions appeared which cleared up spontaneously after a period of 2 years (Evans and Warin, 1957). Foldvari (1935), who preferred the term post-traumatic angioma,

destroyed the lesions by diathermy and no recurrence was noted after several months' observation. Sims *et al.* (1948) considered that the condition was a form of haemangiopericytoma, although it would seem more likely that multiple pyogenic granulomata is a different entity (Cole *et al.*, 1955). Sims's case was that of a 12-year-old boy with satellite lesions which developed after cauterisation of the primary.

The case reported here is unusual as the condition occurred in an adult, the trauma preceding the formation of satellite lesions was minimal and two lesions appeared before any traumatic episode. The main point of interest is that the patient noted that the first skin change was a bluish dusky subcutaneous swelling over the bridge of the nose, which was followed by two small red nodules within the confines of this



FIG. 1.

swelling. It may well be that the additional factor of trauma is necessary for the production of satellite lesions. This case would suggest that there is probably some underlying pathological change, possibly vascular in type, over a relatively larger area of the skin, before the appearance of the classical cherry-red nodules.

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- CANTER, S. (1949) *Brit. J. Derm.*, **61**, 130.
 EVANS, C. D. (1954) *Proc. R. Soc. Med.*, **47**, 1063.
 — and WARIN, R. P. (1957) *Brit. J. Derm.*, **69**, 106.
 FOLDVARI, F. (1935) *Ibid.*, **47**, 463.
 SIMS, C. F., KIRSCH, M. and MACDONALD, R. G. (1948) *Arch. Derm. Syph., Chicago*, **58**, 194.

The following cases also were shown :

Bullous and Nodular Urticaria Pigmentosa.—Dr. N. A. THORNE.

Urticaria Pigmentosa.—Dr. G. C. WELLS.

Urticaria Pigmentosa with Hepatosplenomegaly.—Dr. M. FEIWEL.

Urticaria Pigmentosa with Blisters.—Dr. C. D. CALNAN.

CURRENT LITERATURE.

A CONTRIBUTION TO THE STUDY OF POIKILODERMA (CONCERNING A CASE OF CON-GENITAL POIKILODERMA WITH NAEVOID FEATURES). L. PINCELLI. (1957) *Arch. ital. Derm. Sif.*, 29, 33.

A girl aged 15 suffered from a widespread eruption arranged in a pattern like a linear naevus and more obvious on the left side of the body than the right. The onset, in the first week of life, consisted of erythema and oedema and gave place to the present eruption of erythema, telangiectases, pigmentation and atrophy. The histopathology showed regions of hyperkeratosis and epidermal thickening (no Bowen-like changes are mentioned) and other regions of attenuation and poor coloration of the dermal collagen bundles. She was otherwise healthy and came of healthy stock. A. L.

LEIOMYOMAS OF THE SKIN AND UTERINE FIBROIDS. A. PIREDDA. (1957) *Arch. ital. Derm. Sif.*, 29, 68.

Both diseases occurred in the same patient at the same time.

A. L.

PREDICTION OF SERUM-CHOLESTEROL RESPONSES OF MAN TO CHANGES IN FATS IN THE DIET. A. KEYS, J. T. ANDERSON and F. GRANDE. (1957) *Lancet*, ii, 959.

A further dietetic experiment in which groups of normal men were given several diets containing different fats. Fats studied included butterfat, hydrogenated coconut oil, olive oil, cotton seed oil, sunflower seed oil, safflower oil, fish oil and ordinary mixed food fats. The intake of fats as a percentage of total calories provided from glycerides of saturated, monoethenoid and polyethenoid fatty acids were estimated for each man on each diet.

The changes in serum cholesterol levels do not support the suggestion that a deficiency of essential fatty acids produces a high serum cholesterol level. Correction of high levels of cholesterol in the serum involved a decrease in the most common dietary fats and the substitution of fats high in polyethenoid fatty acids. R. H. M.

FAMILIAL HYPERGAMMAGLOBULINAEMIA AND SYSTEMIC LUPUS ERYTHEMATOSUS. T. LEONHARDT. (1957) *Lancet*, ii, 1200.

This is a report of a family of 14 siblings, three of whom developed systemic lupus erythematosus with raised γ -globulin and five others showed hypergammaglobulinaemia only. The author suggests that in this family there is an inherited abnormality in the mechanism of antibody production that leads to hypergammaglobulinaemia. The formation of injurious antibodies may lead to the development of systemic lupus erythematosus. R. H. M.

LIGATION OF ANKLE COMMUNICATING VEINS IN THE TREATMENT OF THE VENOUS-ULCER SYNDROME OF THE LEG. H. DODD, A. R. CALO, M. MISTRY and A. RUSHFORD. (1957) *Lancet*, ii, 1249.

A report of the follow-up of 174 patients with venous ulcer syndrome treated by ligating ankle communicating veins during a period of over 4 years. Of 96 patients treated more than 2 years ago, 90% had a satisfactory result. The analysis of the results is complicated by the high proportion of patients who had had previous operations for varicose veins. R. H. M.

AN ATYPICAL CARCINOID TUMOUR SECRETING 5-HYDROXYTRYPTOPHAN. M. SANDLER and P. J. D. SNOW. (1958) *Lancet*, i, 137.

The patient described showed flushing attacks precipitated by food, particularly alcohol. The flush was patchy and bright red and could be attenuated by antihistamines. He was found to have a primary carcinoid tumour of the stomach with metastases in the liver. The atypical features of the case consist of the bright red flush instead of the areas of cyanosis, erythema and pallor occurring in the typical carcinoid syndrome, the absence of argentaffin granules in the tumour and the presence of 5-hydroxytryptophan as well as 5-hydroxytryptamine in the urine. R. H. M.

INVOLVEMENT OF THE NERVOUS SYSTEM IN BEHÇET'S DISEASE. A. D. EVANS, C. A. PALLIS and J. D. SPILLANE. (1957) *Lancet*, ii, 349.

ENCEPHALOMYELOPATHY IN BEHÇET'S DISEASE. W. H. McMENEY and B. J. LAWRENCE. (1957) *Lancet*, ii, 353.

The first article describes three patients with Behçet's disease who also showed abnormalities in the nervous system. Although Behçet's disease is usually benign almost half the patients showing involvement of the nervous system have died. In one of the patients reported here a virus was isolated from material taken from the anterior chamber and from brain tissue. Six of eleven patients with Behçet's disease showed a titre of neutralizing antibody to the virus isolated exceeding 1 : 32. Fourteen control subjects showed no virus neutralizing antibody.

The second article describes the pathological findings in two fatal cases of Behçet's disease with nervous system involvement, one being the case described in the previous article from whom a virus was isolated. The pathological findings consisted of multiple small softenings of the central nervous system mainly affecting the brain stem and hypothalamus and occurring in relation to the smaller blood vessels more often in white matter than grey. Myelin loss appeared to be secondary.

R. H. M.

CELLULITIS AND THROMBOPHLEBITIS IN BEHÇET'S SYNDROME. G. R. CARR. (1957) *Lancet*, ii, 358.

Although the initial lesion in this syndrome is usually in the eye or skin and mucous membrane, this patient was first seen because of recurrent thrombophlebitis. He also developed areas of cellulitis.

It is suggested that the latter may be another manifestation of non-specific tissue sensitivity which has been previously reported in this condition.

R. H. M.

CARDIAC INVOLVEMENT IN ANAPHYLACTOID PURPURA. G. A. MACGREGOR and J. VALLENCE-OWEN. (1957) *Lancet*, ii, 572.

Three patients with anaphylactoid purpura showed signs of myocardial damage. Two suddenly developed cardiac failure at the onset of the eruption as well as temporary atrial fibrillation. All the patients showed temporary abnormalities in the E.C.G. Cardiac manifestations may be due to direct involvement of the heart by the purpuric process. Such manifestations may provide an indication for corticosteroid therapy.

R. H. M.

EPIDERMODYPLASIA VERRUCIFORMIS LEWANDOWSKY-LUTZ. S. JABLONSKA and B. MILEWSKI. (1957) *Dermatologica*, 115, 1.

Four cases of epidermodysplasia verruciformis are described which were characteristic both in their clinical course and histology. In the first two, sisters, the eruption appeared after a brother had rubbed on to both of them a squashed wart from his hand. In the other two cases there was no known connection with warts. In the first two cases it was possible under special conditions to make positive auto- and heteroinoculations, while in the other two this could not be attempted, owing to outside circumstances. In one of the first two cases some lesions were made to recede with erythema doses of Bucky irradiation. In the other two, small Bucky doses were ineffective.

These observations suggest that epidermodysplasia verruciformis is a variety of generalized flat warts, probably depending upon the character of the region of skin affected. It is especially stressed that besides a positive autoinoculation, a positive heteroinoculation was successful for the first time on record.

(Slightly modified from authors' summary.)

J. F. S.

LIPOID PROTEINOSIS. I. KATZENELLENBOGEN and H. UNGAR. (1957) *Dermatologica*, 115, 23.

A case of lipoid proteinosis, published by Urbach 28 years ago, has been observed by the authors for 2½ years. The present findings are compared with those formerly recorded. Capillaroscopy shows spasm of many capillaries in the nail-beds and conjunctivae, in their arterial portions, with interruption of blood-flow and petechiae. Histologically, there are degeneration and destruction of the elastic fibres, and hyalinosis of the upper corium, beginning round the arterioles and sweat glands. Further, there is very little or no lipoid in the hyaline nodules and round the vessels. The hyaline contains carbohydrate and probably little or no protein. The slow develop-

ment of the clinical signs with relatively little change over almost 30 years suggests that the syndrome depends on a primary, constitutionally determined disease of the capillaries which leads to a slow degeneration of the elastic fibres.

(Modified from authors' summary.)

J. F. S.

KOEBNER'S PHENOMENON IN A STUDY OF THE PRIMARY EPIDERMAL PATHOGENESIS OF PSORIASIS. A. KUTA and E. NEUMANN. (1957) *Dermatologica*, 115, 51.

In an endeavour to throw light on the vexed question of the site of the primary change in psoriasis, the authors have used the dehydrogenase reaction, which is believed to be a good indicator of the metabolic rate, and particularly of the mitotic activity of a tissue. They scratched the surface of apparently normal skin in psoriatics and in non-psoriatic controls, on the knees, as a site of election, and on the buttocks as less predisposed, and performed biopsies six to nine days later, before psoriasis was clinically apparent in the psoriatics. They did this on one case of lichen planus as well, and also excised a paronychia wart for examination. All biopsies in psoriatics and the lichen planus patient and the wart gave strongly positive reactions, while in the controls all the buttock biopsies were negative, two out of four from the knee negative, as also one from the volar side of the wrist. These findings support the view that the primary change in psoriasis takes place in the epidermis, not in the dermis.

J. F. S.

GROWTH OF CANDIDA ALBICANS ON KERATIN AS SOLE SOURCE OF NITROGEN. L. KAPICA and F. BLANK. (1957) *Dermatologica*, 115, 81.

Experiments in culturing *Candida albicans* on hoof and nail keratin as sole source of nitrogen were done in order to investigate the pathogenicity of this yeast for keratinized tissues.

It was found that:

(1) *C. albicans* can grow on media containing either keratin, salts and glucose, or keratin and glucose.

(2) Glucose is necessary to initiate growth.

(3) Out of three glucose concentrations tested (2, 4 and 8%), best results were obtained with 2% glucose.

The appearance of nitrogenous breakdown products of keratin in culture media was followed for four months qualitatively by ninhydrin tests and paper chromatography and quantitatively by determination of total nitrogen and α -amino nitrogen.

The first amino-acids appeared in the culture liquid 40 days after inoculation. Fourteen amino-acids were identified. The total nitrogen increased during the four months' course of the experiments and was found to include only a small proportion of free amino-acids.

It was thereby proved that *C. albicans* can digest keratin.

Although this purely chemical investigation cannot provide a complete answer to the question of pathogenicity, its results strongly indicate the pathogenicity of *C. albicans* for keratinized tissues. Furthermore, the relationship between sugar metabolism and keratinolytic activities of *C. albicans* corroborates and explains many clinical observations relating cutaneous moniliasis to the sugar-content of keratinized tissues.

(Authors' summary.)

J. F. S.

ELASTICITY OF HUMAN SKIN RELATED TO AGE. L. H. JANSEN and P. B. ROTTIER. (1957) *Dermatologica*, 115, 106.

Simple stretching experiments with strips of skin taken from the abdominal walls in cadavers, show that elasticity of skin is independent of age or sex, when the loads applied do not exceed those realizable at normal clinical examination.

(Modified from authors' summary.)

J. F. S.

CURLY-HAIR NAEVI. W. BORN. (1957) *Dermatologica*, 115, 119.

There are on record a very few cases of areas of curly hair on scalps covered otherwise with straight hair, and Born adds a further case of his own, in a boy of 8. The affected area, of about the size of a child's palm, on the right parietal region, had remained unchanged from the first year of life. The shaved scalp in this region did not differ noticeably from the remainder.

J. F. S.

ULTRASONIC THERAPY IN DERMATOLOGY. F. MAAG. (1957) *Dermatologica*, 115, 121.

The author treated 180 patients, mostly suffering from leg ulcers, x-ray ulcers and acne vulgaris with ultrasonic therapy, and another 37 patients with warts or corns, by means of the so-called

focussed ultra-sound. In x-ray ulceration the results were rather encouraging, but otherwise the conclusion is that ultra-sound has little to offer the dermatologist. J. F. S.

C-REACTIVE PROTEIN IN BLOOD SERUM AND BLISTER FLUID IN VARIOUS DERMATOLOGICAL CONDITIONS. R. ROZANSKY and J. SHANON. (1957) *Dermatologica*, 115, 136.

One hundred and forty-three blood samples and 58 samples of fluid from blisters were tested for the presence of C-reactive protein (CRP). CRP was present in the acute stage of various dermatological conditions. There was a parallelism between elevation of erythrocyte sedimentation rate and CRP concentration in serum. CRP was almost always present in blister fluid when found in blood serum. In 3 cases where CRP was present in the serum in low concentration it could not be detected in blister fluid. CRP was not detected in blister fluid when absent from blood serum. It is concluded that CRP passes from the blood into skin blisters.

(Authors' summary.)

J. F. S.

NEW DATA ON THE MODE OF ACTION OF ATEBRIN. E. NAGY, L. KOCSÁR, I. JOKAY, C. HADHAZY and K. TUZA. (1957) *Dermatologica*, 115, 143.

The authors have carried out experiments on animals in order to investigate the action of Atebrin (Mepacrine). They draw the following conclusions: (1) Atebrin has an antihistamine action, but (2) its effect is not to be explained as a strengthening of anti-histaminase action. (3) Animals pre-treated with Atebrin showed hypertrophy of the adrenal cortex, with increased lipoid production which supports the earlier suggestion of the authors that the adrenal cortex plays a part in the mechanism of the action of Atebrin. There are, however, further factors to be investigated besides the antihistaminic effect.

(Modified from authors's summary.)

J. F. S.

ON THE NATURE OF THE MITSUDA AND THE KVEIM REACTIONS. R. KOOLJ and TH. GERRITSEN. (1958) *Dermatologica*, 116, 1.

Positive Mitsuda reactions were obtained with suspensions of normal liver particles in patients with tuberculoid leprosy. These suspensions gave negative results in patients with lepromatous leprosy. The Mitsuda reactions obtained with these preparations of normal tissue are similar to those obtained with lepromin containing leprosy bacilli.

Bacterial filtrates of lepromin and normal tissue preparations did not evoke a positive Mitsuda reaction in patients with tuberculoid leprosy.

Evidence is adduced that in the Mitsuda reaction we are dealing with a sarcoid (tuberculoid) type of foreign-body reaction or an isomorphic phenomenon.

The Kveim antigen does not contain a specific substance, and the reaction produced is similar to that of a saline tissue extract.

The conclusion arrived at is that the Mitsuda and Kveim reactions are of a similar nature.

With Kveim antigen positive reactions were obtained in patients with tuberculoid leprosy.

It is considered that the Kveim reaction is an expression of a sarcoid mode of reaction in certain individuals.

It is concluded that the disease sarcoidosis is a syndrome, which can be evoked by many agents.

(Authors' summary.)

J. F. S.

THE IDENTIFICATION OF MICROSPORON FELINEUM (FOX AND BLAXALL) BY MEANS OF THE ADDITION OF BOILED EARTH TO THE CULTURE-MEDIUM. P. WENK and H. GELEICK. (1958) *Dermatologica*, 116, 188.

Van Breuseghem in 1952 showed that addition of soil to the culture medium greatly increased the formation of typical reproduction organs in dermatophytes. The authors have improved on this by using a filtrate of boiled earth, which has the advantage of leaving the culture medium transparent, and thus being applicable to the method of culture on slides. In a culture of *Microsporon felineum* from a patient's hair, and one from the hair of a cat, thought to be the source of the infection, they obtained on first sub-culture typical fusiform macroconidia, which established the identification. In the past, macroconidia were often obtained only after repeated sub-culture, and the saving of time may be great.

J. F. S.

ROSACEA-LIKE TUBERCULIDE OF LEWANDOWSKY. W. G. VAN KETEL. (1958) *Dermatologica*, 116, 201.

A study of the literature casts grave doubt on all the supposed criteria for the diagnosis of rosacea-like tuberculide. From the author's own series of 55 cases of rosacea he concludes

that neither the appearances, diascopy, the histology nor the Mantoux reaction justify the view that such a tuberculide exists, and he considers that the name should be abandoned.

J. F. S.

KERATOSIS FOLLICULARIS SERPIGINOSA LUTZ (ELASTOMA INTRAPAPILLARE PERFORANS VERRUCIFORME MIESCHER). K. DAMMERT and T. PUTKONEN. (1958) *Dermatologica*, 116, 143.

The authors describe a further example of the above condition. The patient was a boy aged 16 who had had it from the age of 10. A good conception of the development of the lesion was obtained by studying serial sections of the keratopapular ridges on the nape of the neck and of the adjacent skin. The first change was an increase of elastic tissue in the upper dermis, where there was no evidence of regressive changes; nor did this area show any intrapapillary elastica aggregations or follicular changes. Then followed a keratopapular stage characterized by a necrobiotic and necrotic process, which was accompanied by granulomatous and simple chronic inflammatory changes. Fibrous healing marked the final stage in the process. Most of the excessive elastic tissue had now disappeared, although dense aggregations of elastic tissue were still present in some papillae, where they formed slightly elevated "elastomas".

From these findings the authors conclude that the clinically active keratopapular stage starts deep at the tips of the rete pegs; the excessive elastic tissue invades the epidermis, causing destruction of the involved tissue, and an inflammatory reaction. The cause of the increased elastic tissue is as yet unknown. It is pointed out, however, that in at least six of seven published cases the onset occurred at the prepubertal age of between 9 and 12, and thus hormonal influences may play a part.

(Slightly modified from authors' summary.)

J. F. S.

PEMPHIGUS VULGARIS UNDER PROLONGED MASSIVE TREATMENT WITH ACTH AND CORTISONE. A. DOSTROVSKY and F. C. SULMAN. (1958) *Dermatologica*, 116, 65.

This, which is stated to be the first of a series of studies on the subject, deals with the urinary excretion of 17-ketosteroids and 17-hydroxycorticoids. It contains a large quantity of precise data.

J. F. S.

LIGHT DERMATOSES. F. P. SCOTT and S. M. C. MOLHUYSEN-V. D. WALLE. (1958) *Dermatologica*, 116, 96.

This is a study of the reaction to different wave-lengths of patients suffering from eruptions ascribed to light. Experiments were carried out on 65 patients with a "monochromator". Patients with dermatitis solaris were hypersensitive to the erythema-producing rays. In prurigo aestivalis, patients' sensitivity to these rays was less than in normal subjects. Patients with lupus erythematosus did not show hypersensitivity to sunburn-producing ultraviolet rays, as is generally believed, but they did clearly show increased sensitivity to the long-wave, direct erythema-producing rays.

(Modified from authors' summary.)

J. F. S.

CHEILITIS HERPETICA CHRONICA PEMPHIGOIDES. V. G. RINALDI. (1958) *Dermatologica*, 116, 35.

The author describes a case of chronic pemphigoid cheilitis which he regards as a variant of herpes simplex. It is characterized clinically by the permanent presence of a paraesthesia of the lips, and by constantly reappearing, isolated, fugitive blisters. The histological picture shows rhythmically intermittently formed blisters, mainly of chronic sub-clinical herpes, but with at times blisters of acute herpes. The author tries to explain the singular symptoms pathogenetically as the action of a lysogenic factor on the herpes virus.

(Slightly modified from author's summary.)

J. F. S.

DEFECTIVE EPIDERMAL PROTEIN METABOLISM IN PSORIASIS. PETER FLESCH and ELIZABETH C. JACKSON ESODA. (1957) *Arch. Derm. Syph., Chicago*, 76, 393.

Two abnormal chemical features were found in all psoriasis scales examined: a low free amino nitrogen content and a high sulphhydryl content. This is reflected in an impaired ability to allow fluids to pass through a column of pulverized scales and in a decreased water binding capacity. This appears to be due to a deficient proteolytic enzyme activity in the psoriatic epidermis. As a result there is abnormal cellular decomposition and abnormal utilization of amino acids for keratin synthesis.

J. K.